MJoSHT
Malaysian Journal of Science, Health & Technology
[mjosht.usim.edu.my]

USIM

Case Report

Diagnostic Challenge of Lupus with Overlap Syndrome in an Adolescent: A Case Report

Anu Suria Ganason, Mohd Radzniwan A. Rashid, Fathima Begum Syed Mohideen, Sharifah Najwa Syed Mohamad and Nurul Hayati Chamhuri

Department of Primary Healthcare, Faculty of Medicine and Health Sciences, Universiti Sains Islam Malaysia, Persiaran Ilmu, Putra Nilai, 71800 Nilai, Negeri Sembilan, Malaysia.

Correspondence should be addressed to:
Mohd Radzniwan A. Rashid; mradzniwan@usim.edu.my

Article Info
Article history:
Received: 12 March 2024
Accepted: 4 June 2024
Published:7 October 2024
Academic Editor:
Norsham Juliana

Malaysian Journal of Science, Health & Technology

MJoSHT2024, Volume 10, Issue No. 2
eISSN: 2601-0003

https://doi.org/10.33102/mjosht.v10i2.407

***Abstract*— Lupus with overlap syndrome is an uncommon autoimmune disease that typically affects teenage females. It can present as various symptoms affecting multiple organs. Delay in the diagnosis of lupus will lead to deleterious effects on the implicated adolescents' health. The case report aims to describe the diagnostic challenge of a refractory skin disease leading to a delay in diagnosis and highlight its psychosocial impact. Here, we describe a case of a teenager who presented with poorly controlled chronic dermatitis. The chronic dermatitis was refractory to the first-line therapy of topical steroids and emollients. She was finally diagnosed with lupus and overlap syndrome, confirmed by a skin biopsy. In conclusion, any chronic refractory skin diseases warrant further referral and investigation at the tertiary centre. Assessment of psychosocial in managing chronic skin disease in adolescent is essential as it could implicate their mental health further.**

***Keywords*— autoimmune disease; eczema, lupus erythematosus; case report**

I. INTRODUCTION

Sclerosis-systemic lupus erythematosus (SSc-SLE) overlap syndrome is the presence of both systemic sclerosis and systemic lupus erythematosus, which accounted for 6.8% reported by an epidemiological study [1]. There is a diagnostic challenge among primary care physicians as the cutaneous lupus presentation mimics other diseases [2]. The early and targeted treatment for the disease could alleviate the course and reduce complications. We report a 19-year-old teenage girl who was misleadingly treated as having chronic dermatitis rash since she was young until her current presentation became worse. Accordingly, a skin biopsy, which was performed late, eventually discovered it was consistent with SLE; hence, the diagnosis of SSc-SLE was made.

II. CASE REPORT

A 19-year-old adolescent with an unremarkable family history was referred by a general practitioner to a family

medicine specialist with a recurrent and worsening history of rash involving her face, trunk, upper limb, and lower limb since the age of 10 years old. The rash was dry and scaly and started over her arm, trunk, back and facial region. She also complained of having prolonged skin tightening over the bilateral forearms. In addition, she also complained of prolonged fever for two weeks along with the rash, which was associated with body aches, multiple joint pains, generalised weaknesses and significant hair loss. The dry scaling rash worsens, involving her face, trunk and upper limb. She also had gastroesophageal reflux symptoms and epigastric pain associated with loss of weight and loss of appetite.

She informed the researcher that she had previously made multiple visits to various general practitioners and was informed that she had chronic dermatitis. Her treatment included various emollients and steroid creams, which only provided temporary relief. Further history revealed that this chronic relapsing and unresolved rashes had affected her studies. She was frequently absent during secondary school, with frequent medical certificates obtained from various general practitioners in multiple clinics. She had also abstained from enrolling into university for tertiary education due to her illness. In addition, she had mild depression and low self-esteem due to the unresolved problem. Her father, a driver, and her housewife mother were greatly concerned about her and helped her seek treatment whenever she developed the rash.

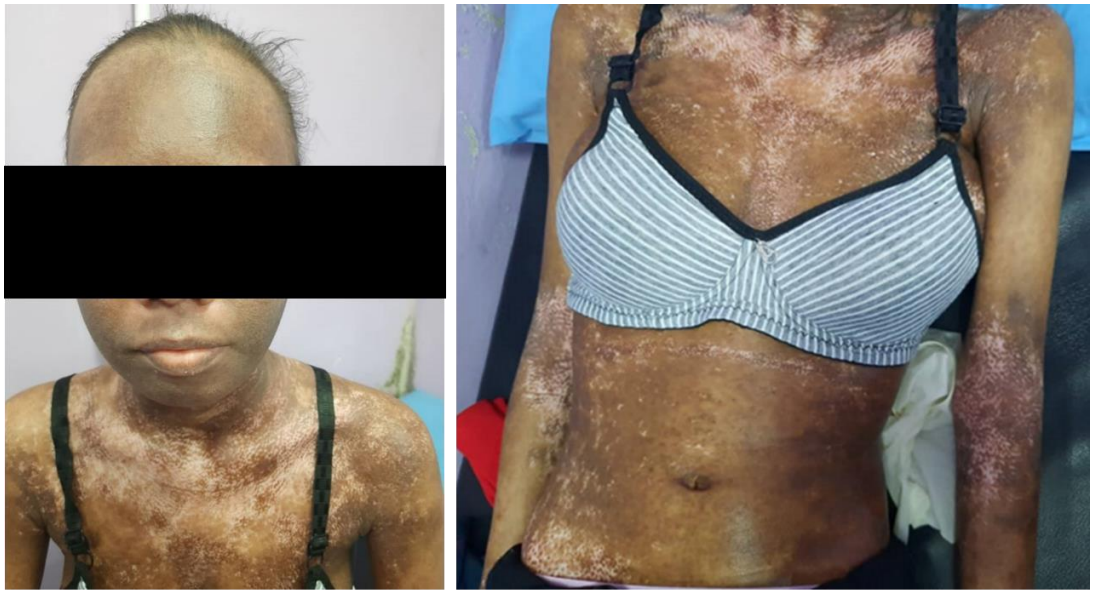
On examination, she was afebrile with a blood pressure of 121/70 mmHg and a pulse rate of 110 beats per minute, irregularly irregular. There were multiple hypopigmented skin lesions, which were scaly, involving her entire body parts, particularly prominent on her palms, face, trunk and back (Figure 1 (a) and (b)). Lung examination revealed minimal bibasal fine crepitations. Meanwhile, the cardiovascular examination presented an ejection systolic murmur over the pulmonary region. Her abdomen was tender over the epigastric region with the presence of hepatosplenomegaly. Moreover, laboratory studies demonstrated bi-cytopenia features, and the liver function test was slightly deranged to normal renal function (Table 1). Her immunological investigations revealed a positive Anti-Nuclear Antibody with a homogenous pattern and a titre of > 1280 and a Nucleolar titre of > 1280. Screening tests for autoimmune hepatitis were otherwise negative (Table 2).

With the above findings, she was then referred to a rheumatologist and dermatologist at a nearby tertiary centre. A skin biopsy was performed, and the presence of basal vacuolar degeneration with dermal mucin was reported, favouring lupus erythematosus. Other immunological markers suggested positive for Anti-Double Stranded DNA (dsDNA), Anti-Ribosomal Positive, Anti-Ro 52, Anti-Ro 60, Anti Cardiolipin antibody, Anti-Beta 2 - Glycoprotein antibodies and Anti-Centromere C (Table 2). Abdomen ultrasound exhibited no features of hepatitis or cholangitis. Additionally, the lung function test was normal. An electrocardiogram (ECG) revealed atrial fibrillation, and an echocardiogram revealed pulmonary hypertension. She was then diagnosed with systemic sclerosis overlapping with scleroderma and cutaneous lupus erythematosus. She was also started on the following medications: hydroxychloroquine tablet 100 mg once daily, prednisolone tablet 10 mg oral daily on a tapering dose, folic acid tablet, amlodipine tablet 2.5 mg daily, calcium carbonate tablet 500 mg od and betamethasone cream 0.05%. Accordingly, she was also referred to the cardiologist.

On subsequent follow-up, her symptoms improved in terms of reduced skin rashes, skin tightening, and reflux symptoms. She regained her appetite and weight. As such, she was more cheerful and determined to continue her studies. Her coping skills were explored, and further reinforcements about her illness and its systemic complications were made.

Table 1. Laboratory Serum Analyses

Test	Reference range (conventional units)	Result
Haemoglobin (g/dL)	12.0-16.0	10.3
Mean corpuscular volume (fl)	76-96	85
Mean corpuscular haemoglobin concentration (pg)	28-34	27
Leukocyte count (/mm^3)	4,000-11,000	3,700
Platelet count (/mm^3)	150,000 – 400,000	248,000
Alkaline phosphatase (IU/L)	38-124	134
Alanine aminotransferase (IU/L)	13- 78	13
Aspartate aminotransferase (IU/L)	< 34	60
Gamma-glutamyl transferase (IU/L)	4-47	125
Total bilirubin (µmol/L)	< 22.0	8.9
Albumin (g/L)	34 - 50	32
Creatinine (mmol/L)	53-88	50



(a) (b)

Figure 1. (a) Hypopigmented rashes appeared on the face and upper trunk of the patient. (b) The patient experienced hypopigmented rashes on the upper limbs and anterior trunk. Written informed consent for the publication of the images was obtained from the patient.

Table 2. Serum Autoimmune Markers

Test	Results
Anti-double stranded DNA	Positive
Anti–ribosomal P	Positive
Anti-Ro 52	Positive
Anti-Centromere	Positive
Anti-Ro 60	Positive
Anti-Cardiolipin antibody	Positive
Anti-B2 Glycoprotein Ab	Positive
Anti-mitochondrial Ab	Negative
Anti-Smooth muscle Ab	Negative
Anti-liver kidney microsome ab	Negative
Anti-Parental Cell Ab	Negative

III. DISCUSSION

Adolescence is a vital phase of identity development. Their physical appearance and disturbances in physical health significantly impact the transition period to adulthood, which may affect their self-confidence. Hence, the delay in diagnosis of lupus with overlap syndrome in this patient has affected her life tremendously.

There is a scarcity of data about SLE diagnosis delay in Malaysia and the Southeast Asian region owing to a lack of nationwide population studies pertaining to SLE [3]. However, the prevalence of diagnosis delay in SLE is reported to be high in developed countries, like the UK, where about 70% of their SLE patients had a delay in their diagnosis [4]. Meanwhile, in America, the prevalence of delayed diagnosis is between 9 to 23% [5].

The interplay between caregiver-related barriers and the healthcare system barriers contributes to delays in diagnosing lupus in the paediatric group. Notably, caregiver-related challenges include difficulties in recognising symptoms, confusing non-specific symptoms with less serious conditions, seeking medical attention only when health worsens, financial constraints related to medical expenses, transportation issues, and missed workdays concerns, and misunderstanding lupus as a contagious disease leading to fear of social stigma. Meanwhile, health system-related obstacles encompass insufficient training among primary healthcare providers, inadequate communication and clinical evaluation. This results in families being sent home without appropriate care, complex healthcare systems necessitating multiple visits before referral to specialists, and misdiagnosis of lupus and its complications [6].

The delay in diagnosis of our patient in this case is multifactorial, and we are in agreement with some of the discussion above. Firstly, the delay in our patient can be attributed to the rarity of the condition. Since it is rare, the doctors attending to the patient failed to detect the diagnosis early. Hence, they continued managing her as chronic eczema despite the unresolved skin condition and development of new symptoms.

Inadequate knowledge in managing difficult skin conditions and inability to perform skin biopsies in primary care clinics are perhaps other reasons resulting in the diagnosis delay. Moreover, the patient's "doctor shopping" behaviour caused the general practitioner to fail to recognise her clinical conditions upon short, infrequent visits. In addition, there was a period of mild skin recovery with over-

the-counter medications. This resulted in false reassurance, as she thought the condition had resolved. Thus, patient education is the key to managing skin conditions.

Dermatitis is an inflammatory skin disorder that causes epidermal changes of dryness, itchiness, and erythema. Note that patients with darker skin are more likely to experience post-inflammatory reactions with hyper- or hypopigmentation. Moreover, cutaneous lupus can be mistaken for chronic dermatitis. In this patient, her presentation was similar to chronic dermatitis, which included flexural skin thickening, hyperkeratosis, scaling, fissuring, excoriation, and hyperpigmentation. A systemic review suggests that there is a higher odds ratio of SLE in a patient with atopic dermatitis (AD) compared to those without AD [7-8].

AD can progress to autoimmune diseases as well [9-10]. It was proposed that genetic components might not be tissue-specific but may share the same immune regulatory mechanisms. Therefore, a skin biopsy would be extremely essential for patients with severe or progressing skin problems. At the same time, moderate to severe chronic dermatitis, which is not resolved by topical treatment and environmental control, should be referred to a tertiary centre for skin biopsy to rule out other differential diagnoses.

Generally, lupus erythematosus has various clinical manifestations. In addition to the clinical symptoms, the diagnostic criteria for SLE in this patient were met with the appearance of a subacute cutaneous lupus rash, a positive immunological marker, and a skin biopsy. As such, constitutional symptoms, mucocutaneous symptoms, and musculoskeletal symptoms are the most prevalent clinical manifestations and the first skin manifestations, respectively. The most common symptoms associated with lupus are musculoskeletal symptoms such as arthralgia, myalgia, and non-erosive inflammatory arthritis [11]. In particular, acute or subacute cutaneous skin lesions are present in 70% to 80% of individuals with lupus. In contrast, overlap syndrome involving SLE and scleroderma accounts for 6.8% of the Asian population, diagnosed at a younger age, less frequently exhibit cutaneous manifestation, and is more frequently associated with arterial hypertension [1]. The patient in this case report presented with cutaneous lupus erythematosus and scleroderma symptoms along with systemic sclerosis features such as Raynaud's phenomenon, reflux phenomenon and skin tightening. Biochemically, the presentation was supported by deranged liver enzymes and positive immunological markers.

In terms of laboratory results, the haematological manifestations observed were leukopenia and anaemia (bi-cytopenia). Her alanine transaminase and aspartate transaminase were also deranged. Immunological markers indicated positive anti-nuclear and anti-SSM antibodies. SLE and AD share several pathophysiological processes. In both AD and SLE, the activation of B cells leads to immune dysregulation and, subsequently, inflammation and tissue damage [3]. Thus, patients with atopic diseases are at significant risk of developing SLE, especially in females.

With regards to the prognosis, according to the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification, SSc-SLE patients exhibited a slightly longer median survival of 26.1 years compared to 22.4 years for those with SLE alone [1]. Furthermore, this epidemiological research indicated that individuals with SSc-SLE often present with lupus anticoagulant, cardiolipin antibody, and pulmonary hypertension [1]. Unfortunately, a delay in diagnosing such a condition would likely lead to a poorer prognosis as it may implicate significant morbidity.

In this patient's case, the delay in the diagnosis not only causes physical trauma but also leads to poorer mental health consequences, including the quality of life. She missed her education and college during this illness. Furthermore, she had developed mild depressive disorder. She also had limited friends and rarely socialised with others during this period of time. Fortunately, after receiving proper management and treatment, as well as continuous empathy and support from her family, friends, and teachers, she managed to pull out from that psychological turbulence, highlighting the vital role of an excellent support system around her. On subsequent follow-ups in our clinic, significant improvements were noted as she appeared to be more cheerful and managed to continue her education. She developed good insight into her illness as well as achieving good coping skills.

VII. CONCLUSIONS

Delaying a diagnosis of lupus with overlap syndrome, especially in the adolescent age, can lead to significant morbidity and mortality in both physical and mental aspects. Therefore, primary care physicians must be more vigilant about the possibility of autoimmune diseases in dealing with unresolved skin problems and should not simply diagnose them as chronic eczema or AD. Notably, hesitancy in referring such cases for a skin biopsy to a tertiary centre, as well as delay in seeking expert opinion when in doubt, should be avoided by primary care doctors. This ensures that an accurate diagnosis can be made and the patient can be managed promptly and successfully.

CONSENT

Written informed consent was obtained from the patient for the anonymised information to be published in this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

ACKNOWLEDGEMENT

We would like to thank the Department of Rheumatology and Department of Dermatology of Hospital Tuanku Ja'afar, Seremban and Polyclinic Universiti Sains Islam Malaysia for their support. We appreciate the patients and family members who provided consent for this study.

REFERENCES

[1] Alharbi, S., Ahmad, Z., Bookman, A. A., Touma, Z., Sanchez-Guerrero, J., Mitsakakis, N., & Johnson, S. R. (2018). Epidemiology and Survival of Systemic Sclerosis-Systemic Lupus Erythematosus Overlap Syndrome. *The Journal of rheumatology*, *45*(10), 1406–1410. https://doi.org/10.3899/jrheum.170953.

[2] Levy, D. M., & Kamphuis, S. (2012). Systemic lupus erythematosus in children and adolescents. *Pediatric clinics of North America*, *59*(2), 345–364. https://doi.org/10.1016/j.pcl.2012.03.007

[3] Tang, S. P., Lim, S. C., & Arkachaisri, T. (2021). Childhood-Onset Systemic Lupus Erythematosus: Southeast Asian Perspectives. Journal of clinical medicine, 10(4), 559. https://doi.org/10.3390/jcm10040559

[4] Kernder, A., Richter, J. G., Fischer-Betz, R., Winkler-Rohlfing, B., Brinks, R., Aringer, M., Schneider, M., & Chehab, G. (2021). Delayed diagnosis adversely affects outcome in systemic lupus erythematosus: Cross sectional analysis of the LuLa cohort. Lupus, 30(3), 431–438. https://doi.org/10.1177/0961203320983445

[5] Rubinstein, T. B., Mowrey, W. B., Ilowite, N. T., Wahezi, D. M., & Childhood Arthritis and Rheumatology Research Alliance Investigators (2018). Delays to Care in Pediatric Lupus Patients: Data From the Childhood Arthritis and Rheumatology Research Alliance Legacy Registry. Arthritis care & research, 70(3), 420–427. https://doi.org/10.1002/acr.23285

[6] Hussain, A., Maheshwari, M. V., Khalid, N., Patel, P. D., & Alghareeb, R. (2022). Diagnostic Delays and Psychosocial Outcomes of Childhood-Onset Systemic Lupus Erythematosus. Cureus, 14(6), e26244. https://doi.org/10.7759/cureus.26244

[7] Ponvilawan, B., Charoenngam, N., Wongtrakul, W., & Ungprasert, P. (2021). Association of atopic dermatitis with an increased risk of systemic lupus erythematosus: A systematic review and meta-analysis. *Journal of postgraduate medicine*, *67*(3), 139–145. https://doi.org/10.4103/jpgm.JPGM_1270_20

[8] Hsiao, Y. P., Tsai, J. D., Muo, C. H., Tsai, C. H., Sung, F. C., Liao, Y. T., Chang, Y. J., & Yang, J. H. (2014). Atopic diseases and systemic lupus erythematosus: an epidemiological study of the risks and correlations. *International journal of environmental research and public health*, *11*(8), 8112–8122. https://doi.org/10.3390/ijerph110808112

[9] Williams, T. S., Aranow, C., Ross, G. S., Barsdorf, A., Imundo, L. F., Eichenfield, A. H., Kahn, P. J., Diamond, B., & Levy, D. M. (2011). Neurocognitive impairment in childhood-onset systemic lupus erythematosus: measurement issues in diagnosis. *Arthritis care & research*, *63*(8), 1178–1187. https://doi.org/10.1002/acr.20489

[10] Holmes, J., Fairclough, L. C., & Todd, I. (2019). Atopic dermatitis and autoimmunity: the occurrence of autoantibodies and their association with disease severity. *Archives of dermatological research*, *311*(3), 141–162. https://doi.org/10.1007/s00403-019-01890-4

[11] National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Selected Immune Disorders and Disability. (2022). *Selected Immune Disorders and Disability*. National Academies Press (US).