CASE REPORT

DOI: 10.4274/hamidiyemedj.galenos.2022.95967

Hamidiye Med J 2022;3(3):205-208

An Unusual Initial Manifestation of Juvenile Systemic Lupus Erythematosus: Chronic Autoimmune (Spontaneous) Urticaria

Jüvenil Sistemik Lupus Eritematozusun Nadir Bir Başlangıç Bulgusu: Kronik Otoimmün (Spontan) Ürtiker

Fatma Gül Demirkan, Özlem Akgün, Vafa Guliyeva, Nuray Aktay Ayaz

İstanbul University, İstanbul School of Medicine, Department of Pediatric Rheumatology, İstanbul, Türkiye

ABSTRACT

Itchy urticarial lesions frequently affect patients and causing considerable distress and impact on daily activities and quality of life. Although chronic autoimmune urticaria (CAU) has been reported as one of the initial manifestations of adult-onset systemic lupus erythematosus (SLE), it is not a common symptom that springs to mind in juvenile systemic lupus erythematosus (jSLE). Here, we report the case of a girl with jSLE suffering from CAU. A 17-year-old girl was referred to the pediatric rheumatology outpatient clinic for CAU lasting 120 days. During her examinations in dermatology and pediatric gastroenterology clinics, antinuclear antibodies were also positive (1:640 dense fine-spotted pattern) and there was a decrease in complement levels. As proteinuria was 4.5 g/day, kidney biopsy was performed and it was compatible with class-IV lupus nephritis. This was followed sequentially by the diagnosis of SLE. The skin lesions disappeared after treatment with methylprednisolone and hydroxychloroquine. She also received cyclophosphamide monthly for renal involvement. CAU is very rare and may be the first sign of lupus, especially associated with the presence of autoantibodies. This case highlights the importance of evaluation for connective tissue diseases such as pediatric lupus, when investigating the etiology of CAU. Early diagnosis and proper treatment is pivotal to prevent morbidities.

Keywords: Urticaria, juvenile systemic lupus erythematosus, hypocomplementemia

ÖZ

Kaşıntılı ürtikeryal döküntüler kişilerin yaşam kalitesini ve günlük aktivitelerini belirgin şekilde etkileyebilmektedir. Kronik otoimmün ürtiker (KOÜ), erişkin başlangıçlı sistemik lupus eritematozusun (SLE) ilk belirtilerinden biri olarak bildirilmiş olmasına rağmen, juvenil sistemik lupus eritematozusta (jSLE) akla gelen yaygın bir semptom değildir. Burada, KOÜ etiyolojisinde jSLE tanısı alan bir kız olguyu sunuyoruz. On yedi yaşında bir kız çocuğu KOÜ (120 gün süren) nedeniyle çocuk romatoloji polikliniğine yönlendirildi. Dermatoloji ve pediyatrik gastroenteroloji kliniklerindeki tetkikleri sırasında antinükleer antikorları da pozitifti (1:640 yoğun ince benekli patern). Hastanın başvurusunda kompleman seviyelerinde azalma vardı. Proteinüri 4,5 g/gün olduğu için böbrek biyopsisi yapıldı ve sınıf IV lupus nefriti ile uyumlu bulundu. Mevcut bulgularla hasta SLE tanısı aldı. Metilprednizolon ve hidroksiklorokin ile tedaviden sonra deri lezyonları kayboldu. Ayrıca böbrek tutulumu için aylık siklofosfamid tedavisi almaktadır. KOÜ oldukça nadirdir ve özellikle otoantikorların varlığı ile ilişkili lupusun ilk belirtisi olabilir. Bu olgu, KOÜ etiyolojisi araştırılırken pediyatrik lupus gibi bağ dokusu hastalıklarının değerlendirilmesinin önemini vurgulamaktadır. Morbiditeleri önlemek için erken tanı ve uygun tedavi çok önemlidir.

Anahtar Kelimeler: Ürtiker, juvenil sistemik lupus eritematozus, hipokomplementemi

Introduction

Hives (medical nomenclature as *urticaria*) is a common critical symptom leading to hospital *admissions worldwide*. The prevalence of urticarial lesions that occur at one or more times during a lifetime is estimated to be over 10% of children. Based on its duration, urticaria is classified as acute or chronic (1). Chronic urticaria is further subclassified as spontaneous (CSU) and inducible. CSU is defined as the occurrence of wheals, angioedema (AE), or both for >6 weeks (1). It is substantial to perform optimal diagnostic workup to reveal the underlying causes of CSU accurately

Address for Correspondence: Nuray Aktay Ayaz, İstanbul University, İstanbul School of Medicine, Department of Pediatric Rheumatology, İstanbul, Türkiye
Phone: +90 532 621 22 14 E-mail: nurayaktay@gmail.com **ORCID ID:** orcid.org/0000-0003-3594-7387
Received: 17.08.2022 **Accepted:** 04.10.2022

for achieving the best management of the patient. CSU may have a link with autoimmune disorders like autoimmune thyroiditis, yet the relationship with juvenile systemic lupus erythematosus (jSLE) has not been clarified (2).

jSLE is a multisystem disease affecting several organs including mucocutaneous tissues. It is characterized by the loss of immune tolerance to self-antigens and dysregulation of autoantibody production (3). Investigation of cutaneous manifestations revealed that the skin involvement including CSU is pretty much among the patients with SLE. Although the prevalence of CSU-like rash is reported as 4.5-12% in jSLE, there is still a lack of information on the spectrum and prevalence of CSU in jSLE and vice versa (2,4).

Recent literature has reported that neutrophilic urticaria or urticaria with predominantly neutrophilic infiltrates may be a predictor for SLE. In addition, based on the similarities of immunoglobulin (Ig) G and IgE mediated autoreactivity, there are reports linking inflammation and autoimmunity related to the pathogenesis of CSU and SLE (5).

Herein, we aimed to report an unusual case of onset of jSLE complicated with nephritis, emphasizing that jSLE can be a predictable diagnosis in the presence of CSU. Informed consent is obtained from the parents of the patient.

Case Report

In October 2021, a 17 year-old girl presented with recurrent attacks of widespread urticaria accompanied by moderate pruritus lasting for two months. Urticarial plaques were variable in size, without AE or vasculitis. The case was evaluated in a dermatology outpatient clinic and she was given antihistaminic (cetirizine, 10 mg/daily) therapy for about 1 month. Although a partial response was achieved, hives continued with relapses and remissions. No other allergic or autoimmune conditions were reported. There was no rheumatic or allergic conditions in her family history. Her medical history revealed that she had widespread joint pain and myalgia for 6 months and had photosensitivity aggravated by sunlight exposure.

In the physical examination, there was abrasion in her nasal mucosa and movements of the right hand was painful. Other system examinations were normal. Her urticarial rashes are demonstrated in Figure 1A and 1B. Her laboratory exams including complete blood count (white blood cell: $6.7x10^9$/L, platelet: $326x10^9$/L), renal function tests, and urinalysis were normal. Although C-reactive protein was in the normal range (4.19 mg/L), erythrocyte sedimentation rate was abnormally high (61 mm/h). Complement levels also displayed abnormality as follows: C3c was 63.6 mg/dL (80-200) and C4 was 3.4 mg/dL (10-40).

Pathologic examination of a punch-biopsy from hives revealed neutrophilic dermatoses. Immunological tests were as follows: Antinuclear antibodies 1:1250 (dense fine speckled pattern), anti-Sm and anti-RNP antibodies positive; however, negative for anti-double stranded DNA, anti-Ro, anti-La, anti-cardiolipin and anti-phospholipid antibodies. Abdominal ultrasonography and echocardiographic evaluation were normal.

Diagnosis of CSU due to jSLE was established and hydroxychloroquine treatment with a dosage of 200 mg/daily was initiated. Her uveal examination was normal and Schirmer test was negative. The systemic lupus erythematosus disease activity index (6) score was 18 (high activity) at the time of diagnosis.

As 24-hour urinalysis revealed 4.5 gr/day proteinuria, kidney biopsy was performed, revealing class IV-G disease (diffuse proliferative nephritis). According to agreed decision of the pediatric nephrology and rheumatology departments, pulse metilprednisolon (1 gr/daily) therapy for 3 consecutive days and intravenous cyclophosphamide (750 mg/m^2) was initiated as induction treatment. She is under prednisone (1 mg/kg/day), hydroxychloroquine (5 mg/kg/day), and cyclophosphamide (750 mg/m^2/monthly) treatment and ultraviolet-light protection by sunscreen.

Discussion

The cutaneous features of SLE are classified as LE-specific and LE-non-specific lesions based on histopathological findings according to the Gilliam and Sontheimer (7) classification. Malar rash and discoid rash are specific skin lesions while Raynaud's phenomenon, cutaneous vasculitis, alopecia, and urticaria are nonspecific lesions. Urticaria may present as the first complaint before the classical form of jSLE emerges (8). The two most common manifestations

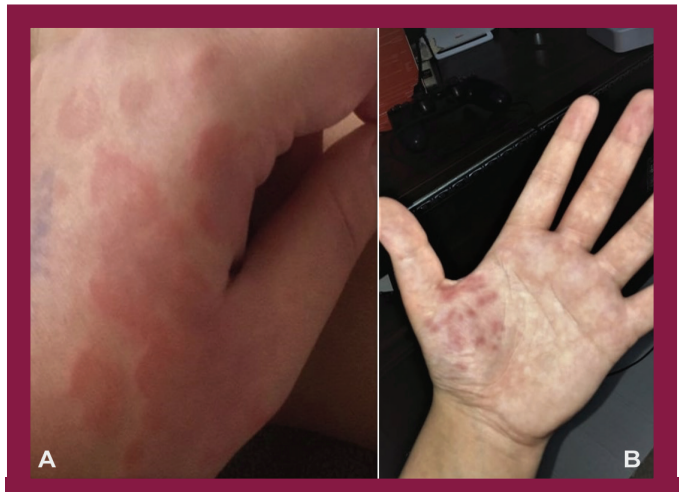

Figure 1A, B. Urticarial vasculitis. Scattered, violaceous, edematous plaques on the upper extremities

of urticarial rash in SLE are CSU and urticarial vasculitis (9). Although urticarial vasculitis resembles CSU it differs in many aspects; lasting longer (>24 h), accompanying by residual pigmentation, burning of the skin rather than itching, and systemic symptoms such as fever, arthralgia and abdominal pain (9). Hypocomplementaemia can present in 18-32% of urticarial vasculitis and indicates a more severe disease (5). CSU is frequently characterized by relapses and remissions, and in several cases clinical features of CSU and jSLE may almost overlap.

In 2018 a nationwide population-based study in Taiwan evaluated the risk of jSLE with a prior clinical diagnosis of urticaria (4). A significant association was found between clinically diagnosed urticaria and jSLE, with a stronger risk associated with more frequent episodes of urticaria (≥3 visits, odds ratio: 2.33, 95% confidence interval 1.91-2.84). In a study by Spadoni et al. (10), during 27 consecutive years, 2 (0.7%) of 271 jSLE patients had chronic, autoimmune urticaria as the first manifestation. Two of them (0.7%) had chronic and painless autoimmune urticaria as the first manifestation of jSLE. In our case, urticarial rashes with flares and remissions were precursors of jSLE. Patients with CSU or urticarial vasculitis may be both harbingers of jSLE. Clinicians should be aware that urticaria may be an early manifestation of jSLE, even in the absence of SLE-specific serologic markers. Although CSU is usually associated with anti-thyroid antibodies in the literature (11,12), thyroid function tests were normal and anti-thyroid antibodies were absent in our case. Drugs used in the treatment of lupus can also trigger CSU. However, in a large cohort study of 852 childhood onset systemic lupus erythematosus by Ferriani et al. (9), none of the patients received lupus treatment at the onset of CSU. They indicated that CSU may be linked to active jSLE, with a predominance of mucocutaneous and musculoskeletal involvement as in our case.

This case report reinforces the importance of a rigorous follow-up of children and adolescents with autoimmune urticaria due to the possibility of concomitant connective tissue diseases. jSLE is one of the pathologies that the clinician should consider, particularly in the differential diagnosis of CSU in children (Figure 2) (1).

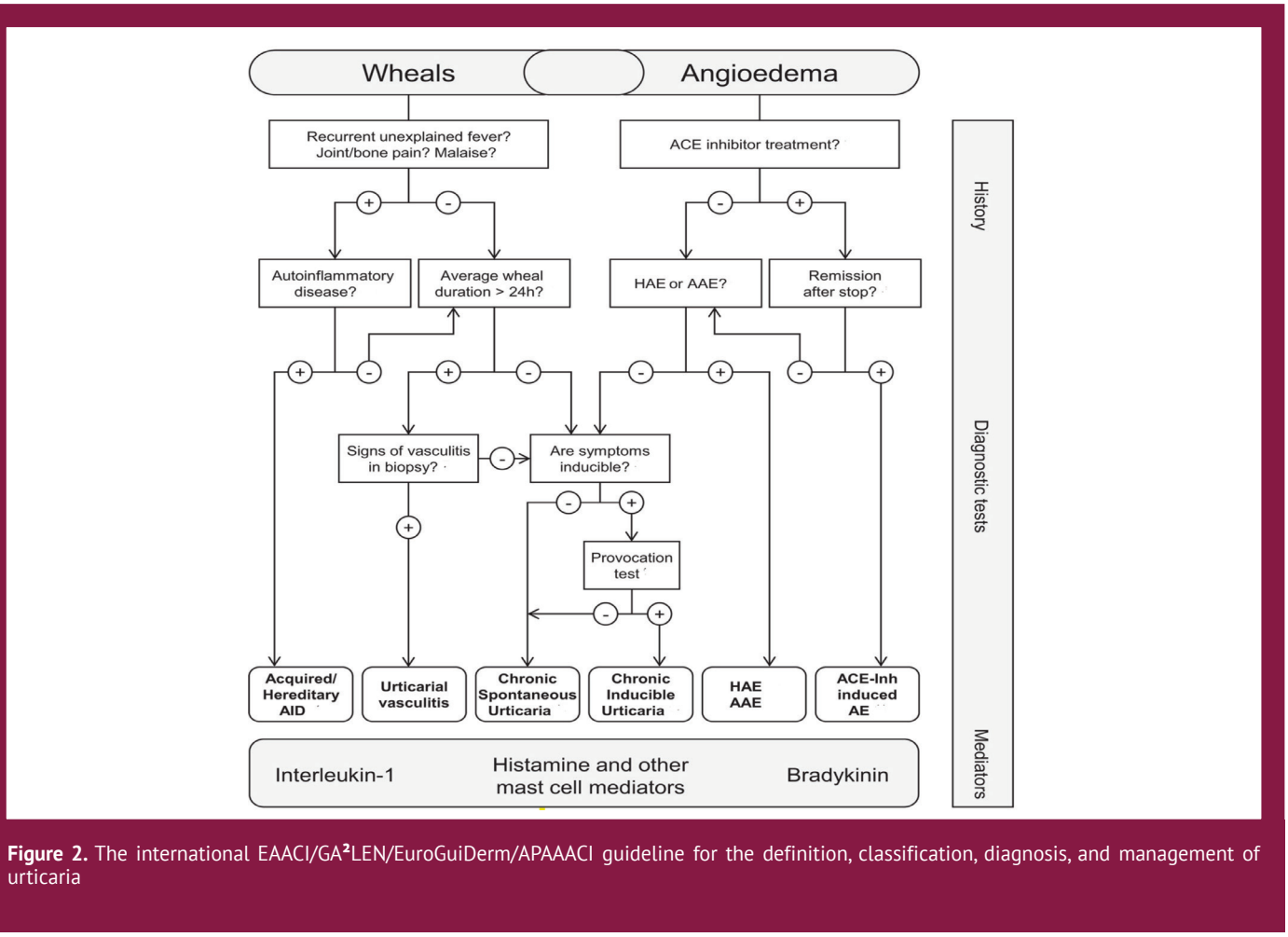

Figure 2. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria

Ethics

Informed Consent: Informed consent was received from the family.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.G.D., Ö.A., V.G., N.A.A., Concept: F.G.D., Ö.A., V.G., N.A.A., Design: F.G.D., Ö.A., V.G., N.A.A., Data Collection or Processing: F.G.D., Ö.A., V.G., N.A.A., Analysis or Interpretation: F.G.D., Ö.A., V.G., N.A.A., Literature Search: F.G.D., Ö.A., V.G., N.A.A., Writing: F.G.D., Ö.A., V.G., N.A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77:734-766. [Crossref]
2. Kolkhir P, Pogorelov D, Olisova O, Maurer M. Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus--a systematic review. Clin Exp Allergy. 2016;46:275-287. [Crossref]
3. Smith EMD, Lythgoe H, Midgley A, Beresford MW, Hedrich CM. Juvenile-onset systemic lupus erythematosus: Update on clinical presentation, pathophysiology and treatment options. Clin Immunol. 2019;209:108274. [Crossref]
4. Lin CH, Hung PH, Hu HY, Chung CJ, Chen TH, Hung KY. Clinically diagnosed urticaria and risk of systemic lupus erythematosus in children: A nationwide population-based case-control study. Pediatr Allergy Immunol. 2018;29:732-739. [Crossref]
5. Saeb-Lima M, Charli-Joseph Y, Rodríguez-Acosta ED, Domínguez-Cherit J. Autoimmunity-related neutrophilic dermatosis: a newly described entity that is not exclusive of systemic lupus erythematosus. Am J Dermatopathol. 2013;35:655-660. [Crossref]
6. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29:288-291. [Crossref]
7. Gilliam JN, Sontheimer RD. Skin manifestations of SLE. Clin Rheum Dis. 1982;8:207-218. [Crossref]
8. Charras A, Smith E, Hedrich CM. Systemic Lupus Erythematosus in Children and Young People. Curr Rheumatol Rep. 2021;23:20. [Crossref]
9. Ferriani MP, Silva MF, Pereira RM, Terreri MT, Saad Magalhães C, Bonfá E, et al. Chronic Spontaneous Urticaria: A Survey of 852 Cases of Childhood-Onset Systemic Lupus Erythematosus. Int Arch Allergy Immunol. 2015;167:186-192. [Crossref]
10. Spadoni M, Jacob C, Aikawa N, Jesus A, Fomin A, Silva C. Chronic autoimmune urticaria as the first manifestation of juvenile systemic lupus erythematosus. Lupus. 2011;20:763-736. [Crossref]
11. DeAmicis T, Mofid MZ, Cohen B, Nousari HC. Hypocomplementemic urticarial vasculitis: report of a 12-year-old girl with systemic lupus erythematosus. J Am Acad Dermatol. 2002;47(Suppl 5):S273-274. [Crossref]
12. Erdem Y, Altunay I, Ozkur E, Sivaz O. The Etiological Evaluation of Patients with Chronic Urticaria. Sisli Etfal Hastan Tip Bul. 2020;54:424-427. [Crossref]