CASE REPORT OLGU SUNUMU

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Severe Cutaneous Eruption in a Woman After Ingesting Multiple Drugs: A Rare Presentation of Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis-Like Lupus Erythematosus

Bir Kadın Olguda Çoklu İlaç Maruziyeti Sonrası Gelişen Şiddetli Kutanöz Erüpsiyon: Stevens-Johnson Sendromu/Toksik Epidermal Nekroliz Benzeri Lupus Eritematozusun Nadir Bir Prezentasyonu

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ABSTRACT Toxic epidermal necrolysis-like lupus erythematosus (TEN-LE) is a very rare variant of LE, which is characterized by extensive areas of epidermal necrolysis indistinguishable from drug induced Stevens-Johnson syndrome (SJS)/TEN. Here, we describe an unusual presentation of LE, in whom acute epidermal necrolysis was the initial diagnostic manifestation of LE. Our patient fulfilled the criteria for a definite diagnosis of systemic LE, in addition she had a history of recent exposure to multiple drugs, some of which are known to cause SJS/TEN and some of which are known to cause drug-induced subacute cutaneous LE. This case report not only discloses an exceptional presentation of SJS/TEN-like LE, but also questions the underlying pathogenic mechanisms of LE.

Keywords: Toxic epidermal necrolysis-like lupus erythematosus; Stevens-Johnson syndrome; systemic lupus erythematosus; drug

ÖZET Toksik epidermal nekroliz benzeri lupus eritematozus [toxic epidermal necrolysis-like lupus erythematosus (TEN-LE)], ilaç ilişkili Stevens-Johnson sendromu (SJS)/TEN'den ayrımın oldukça zor olduğu, geniş vücut alanlarında epidermal nekrolizin izlendiği, LE'nin oldukça nadir bir varyantıdır. Burada, akut epidermal nekrolizin LE'nin ilk diagnostik manifestasyonu olduğu sıra dışı bir olguyu sunuyoruz. Olgumuz sistemik LE'nin majör tanı kriterlerini karşılamak ile birlikte, yakın zamanlı çoklu ilaç maruziyeti tariflemekte idi. Bu ilaçların bir kısmı SJS/TEN, bazıları ise ilaç ilişkili subakut kutanöz LE'nin bilinen etiyolojik faktörleri arasındadır. Bu vaka sunumu ile SJS/TEN benzeri LE'nin ilginç bir prezentasyonunu sunarken, LE gelişiminde rol oynayan patojenik mekanizmaları sorgulamaktayız.

Anahtar Kelimeler: Toksik epidermal nekroliz benzeri lupus eritematozus; Stevens-Johnson sendromu; sistemik lupus eritematozus; ilaç

Toxic epidermal necrolysis-like lupus erythematosus (TEN-LE) is a very rare variant of LE characterized by severe epidermal necrolysis. It is challenging to distinguish TEN-LE from drug-induced Stevens-Johnson syndrome (SJS)/TEN because the phenotypic expression of both conditions is similar.[1-3] Here, we describe an atypical presentation of LE in which acute epidermal necrolysis was the initial diagnostic manifestation of LE. Our patient met the criteria for a definite diagnosis of systemic LE (SLE).[4] She also had a history of recent exposure to multiple drugs, some of which have been linked to SJS/TEN[5] and others to drug-induced subacute cutaneous LE (DISCLE).[6]

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CASE REPORT

A 40-year-old woman presented with redness and tenderness on her face and painful mouth erosions. She had just been diagnosed with hypertension and a urinary tract infection, for which she was administered a variety of drugs, including perindopril/indapamide, valsartan/hydrochlorothiazide, ceftriaxone, and fosfomycin, only days before her admission. Her detailed medical history revealed a history of pancytopenia for one year, arthralgia for several months, frontal fibrosing alopecia for 6 months and antinuclear antibody (ANA) positivity (1:1000, homogenous), which was detected three months before the presentation. Her comprehensive medication history revealed a recent use of perindopril/indapamide combination, which was introduced ten days before the eruption (received for three days, quitted due to lymphocytopenia) and usage of valsartan/hydrochlorothiazide combination, which was introduced seven days before the eruption (received for seven days) and usage of cefuroxime axetil, which was introduced seven days before the eruption (received for 7 days) and a single dose usage of fosfomycin, which was received just before the eruption (Table 1).

The initial dermatological examination of the patient was as follows: band-like hairline recession and lonely hairs on the front and sides of the scalp, bilateral partial eyebrow alopecia, edematous and violaceous erythema on the face with erosions and denuded epithelium, in which periorificial areas were spared, erythematous macules on the frontal neck, hyperemia and vesicles on the palatal region, erosions with pseudomembranes on bilateral buccal mucosa, an erosion with hemorrhagic crust on the upper labial mucosa. The Nikolsky sign was positive and there were no signs of eye and genital involvement (Figure 1, Figure 2) (Table 1). The patient was admitted to the hospital on suspicion of SJS/TEN, and 1 mg/kg/day systemic prednisolone was prescribed. The face lesions increased in the following days, displaying a remarkable photo-distributed pattern. The follow-up dermatological examination (3rd day of the admission) of the patient was as follows: edema of the face increased, large bullae with serous fluid appeared on the chin, anterior neck and ears, the eruption widened, new lesions appeared on the ears, trunk and upper extremities, periorificial sparing disappeared, photodistributed pattern of the eruption became obvious with a sharp demarcation, which spared lateral aspects of the forehead, temples and shadowed areas of the neck. The color of the eruption darkened; a deeper violaceous hue became apparent. Hemorrhagic erosions appeared on the entire oral mucosa. Atypical targetoid lesions appeared on the distal upper extremities, especially on palms. There was ocular involvement (Figure 1) (Table 1). On the 5th day of admission large areas of epidermal detachment involving 10-30% of the body surface area.

We evaluated a dermatosis with a photosensitive component, and serological tests indicated results consistent with LE. Laboratory investigations of the patient were as follows: hemoglobin: 10.1 g/dL (n: 12-15.6), hematocrit: 33.2% (n: 35.5-45.5), lymphocyte count: 0,72 x 10^9/L (n: 1.1-4.5), lymphocyte percentage: 9.5% (n: 20-44), urea: 111 mg/dL (n: 19-49), creatinine: 1,21 mg/dL (normal range: 0.5-1.1), C-reactive protein: 67.10 mg/L (n: 0-5), erythrocyte sedimentation rate: 119 mm/hr (n: 0-20), complement C3c (C3c): 0.4 g/L (n: 0.9-1.8), peripheral blood smear: anisopoikilocytosis, direct coombs: ++, thyroid stimulating hormone: 6.25 mU/L (n: 0,55-4,78), anti-thyroglobulin antibody: 113.3 IU/mL (cut-off for autoimmune thyroid disease: >=4,5 IU/mL), anti-thyroid peroxidase antibody: 308 U/mL (n: <60), 24 hour urine microalbumin: 2205,75 mg/24 hr (n: <30), 24-hour urinary protein: 5458 mg/24 hr (n: 150), ANA: 1:320 (positive, homogenous pattern), anti-double-stranded DNA (anti-dsDNA): 126,74 RU/mL (positive) (≥100: positive), anti-Ro/SSA: positive (++), nucleosome: border positive (+), anti-ribosomal P antibody: positive (+++), anti-mitochondrial M2 antibody: positive (++) (Table 1).

A lesional skin biopsy, which was performed from a lesion on the trunk, demonstrated focal full-thickness apoptosis of the epidermis, basal vacuolar degeneration, mild dermal lymphocytic infiltration. A renal biopsy revealed global glomerulosclerosis, periglomerular fibrosis, glomerular basement membrane thickening, mild lymphocyte infiltration of the renal interstitium. The patient also had symptoms of

TABLE 1: Clinical and laboratory profile of the patient.

History	• Pancytopenia for one year • Arthralgia for several months • FFA for 6 months • ANA positivity (1:1000, homogenous) detected three months before the presentation • Urinary tract infection, recent diagnosis • Hypertension, recent diagnosis
Medication history	• Perindopril/indapamide combination; introduced ten days before the eruption, received for three days, quitted due to lymphocytopenia • Valsartan/hydrochlorothiazide combination; introduced seven days before the eruption, received for seven days • Cefuroxime axetil; introduced seven days before the eruption, received for seven days • Fosfomycin; single dose before the eruption
Initial presentation	• Band-like hairline recession and lonely hairs on the front and sides of the scalp, bilateral partial eyebrow alopecia • Edematous and violaceous erythema on the face with erosions and denuded epithelium, periorificial areas were spared • Erythematous macules on the frontal neck • Hyperemia and vesicles on the palatal region, erosions with pseudomembranes on bilateral buccal mucosa, an erosion with hemorrhagic crust on the upper labial mucosa • No signs of eye and genital involvement • Nikolsky sign positive
Follow-up dermatological examination (3^{rd} day of the admission)	• Edema of the face increased, large bullae with serous fluid appeared on the chin, anterior neck and ears • The eruption widened, new lesions appeared on the ears, trunk and upper extremities • Periorificial sparing disappeared, photodistributed pattern of the eruption became obvious with a sharp demarcation, which spared lateral aspects of the forehead, temples and shadowed areas of the neck • The color of the eruption darkened, a deeper violaceous hue became apparent • Hemorrhagic erosions appeared on the entire oral mucosa • Atypical targetoid lesions appeared on the distal upper extremities, especially on palms • Eye involvement
Follow-up dermatological examination (5^{th} day of the admission)	• Large areas of epidermal detachment involving 10-30% of the BSA
Laboratory results with significance	• Hb: 10.1 g/dL (n: 12-15.6)*, Hct: 33.2% (n: 35.5-45.5)* • Lymphocyte count: 0.72 x 109/L (n: 1.1-4.5)*, lymphocyte percentage: 9.5% (n: 20-44)* •Urea: 111 mg/dL (n: 19-49)**, creatinine: 1,21 mg/dL (normal range: 0.5-1.1)** • CRP: 67.10 mg/L (n: 0-5)** • ESR: 119 mm/hr (n: 0-20)** • C3c: 0.4 g/L (n: 0.9-1.8)* • Peripheral blood smear: anisopoikilocytosis • Direct coombs: ++ • TSH: 6.25 mU/L (n: 0,55 - 4,78)** • Anti-TgAb: 113.3 IU/mL (cut-off for autoimmune thyroid disease: >=4,5 IU/mL)**, anti-TPO: 308 U/mL (n: <60)** • 24 hour urine microalbumin: 2205,75 mg/24 hr (n: <30)**, 24-hour urinary protein: 5458 mg/24 hr (n: 150)** • ANA: 1:320 (positive, homogenous pattern) • Anti-dsDNA: 126,74 RU/mL (positive) (≥100: positive) • Anti-Ro/SSA: positive (++) • Nucleosome: border positive (+) • Anti-Rib-P: positive (+++) • AMA-M2: positive (++)
Histopathological examinations	• Skin biopsy: Focal full-thickness apoptosis of the epidermis, basal vacuolar degeneration, mild dermal lymphocytic infiltration • Renal biopsy: Global glomerulosclerosis, periglomerular fibrosis, glomerular basement membrane thickening, mild lymphocyte infiltration of the renal interstitium

*Decreased; **Increased; FFA: Frontal fibrosing alopecia; ANA: Antinuclear antibody; BSA: Body surface area; Hb: Hemoglobin; Hct: Hematocrit; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; C3c: Complement C3c; TSH: Thyroid stimulating hormone; Anti-TgAb: Anti-thyroglobulin antibody; Anti-TPO: Anti-thyroid peroxidase antibody; Anti-dsDNA: Anti-double-stranded DNA; Anti-Rib-P: Anti-ribosomal P antibody; AMA-M2: Anti-mitochondrial M2 antibody.

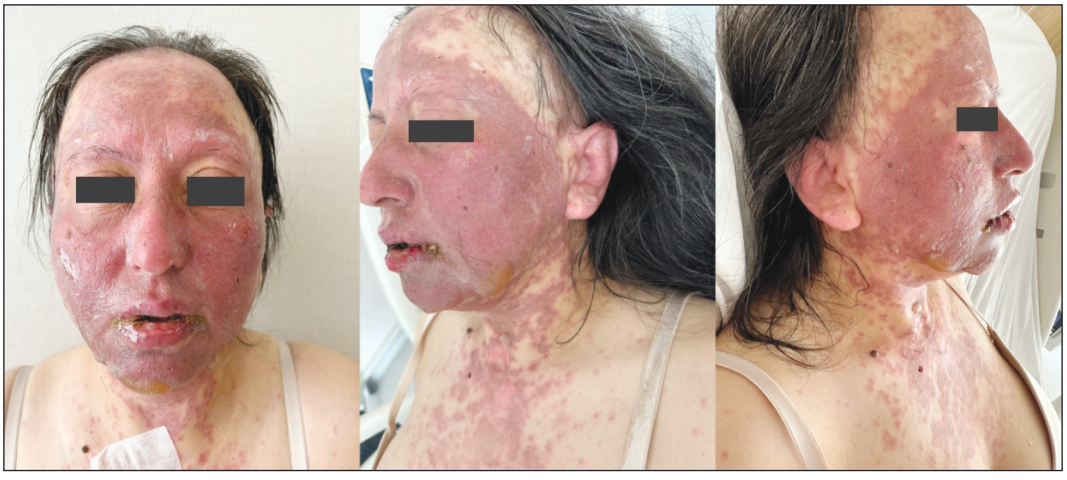

FIGURE 1: Violaceous erythematous eruption on the head and trunk of patient. Note the remarkable photo-distributed pattern.

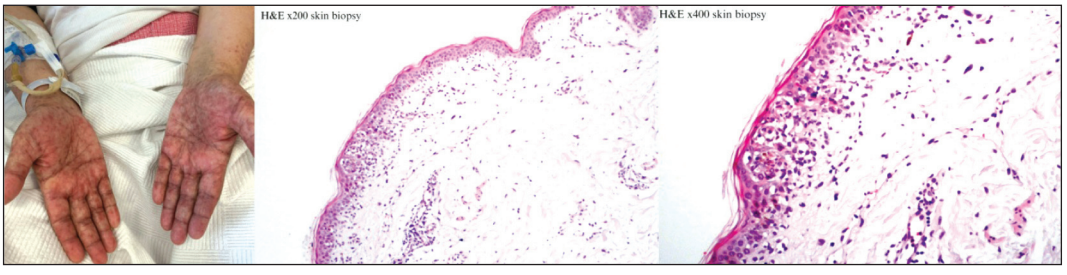

FIGURE 2: Pamoplantar lesions and histopathology of the case.

nephritis and hemolytic anemia, which was diagnosed on the clinical, laboratory and histopathological examinations. Thus, intravenous immunoglobulin treatment was initiated. The patient gradually recovered after receiving intravenous immunoglobulin and 200 mg of hydroxychloroquine daily. Informed consent and permission for publication of medical images and clinical details were taken from the patients.

DISCUSSION

The patient presented here met the criteria for a definitive diagnosis of SLE.[4] Her eruption had typical features of TEN-LE, with a distinct photo distribution and palmar lesions.[1-3] Although evident photo distribution favors a diagnosis of TEN-LE over SJS/TEN, initial photo-distributed lesions have been reported in cases of SJS/TEN, which are induced by phototoxic medications, a well-known of which is hydrochlorothiazide.[1,7] The involvement of palms/soles is a valuable finding when differentiating TEN-LE from drug-induced SJS/TEN because palmoplantar lesions are typically absent in the latter.[3] According to a recent report, characteristic features of TEN-LE include the absence of "high-risk" drug use, a photo-distributed eruption, insidious onset of symptoms, minimal mucosal involvement, and autoimmune serology consistent with SLE.[1] However, 47% of TEN-LE patients were given a new medication before the eruption, and some had severe mucosal involvement.[1,3] Although most patients with TEN-LE experience a gradual subacute progression, the eruption can occur rapidly within days in some patients, particularly those with apparent SLE activity.[1,2]

Whether this cutaneous eruption is due to SJS/TEN, a preceding LE exacerbation, or a combination of both is unclear. The drug causality algorithm for epidermal necrolysis leads to cephalosporins, which include cefuroxime axetil, as a possible/very likely cause.[5] Although rare, SJS/TEN has been reported with the administration of fosfomycin, perindopril/indapamide, and valsartan/hydrochlorothiazide.[8,9] If we assume SJS/TEN in

our patient with a preceding (S)LE exacerbation, which drug caused which? Is SJS/TEN caused by cefuroxime axetil or fosfomycin? Is the cause of the LE flare perindopril/indapamide or valsartan/hydrochlorothiazide? Angiotensin-converting enzyme inhibitors and thiazide diuretics, particularly hydrochlorothiazide, are well-known causes of DISCLE but not SLE.[6] Drug-induced lupus erythematosus (DILE) differs from idiopathic SLE. Patients with DILE develop lupus-like symptoms months to years after exposure to the causative drugs. In contrast to idiopathic SLE, DILE does not have a young female predominance. It is characterized by fever, weight loss, and musculoskeletal symptoms, with no central nervous system, renal, or hematological abnormalities. Antihistone and antichromatin antibodies are commonly positive in DILE, whereas anti-dsDNA antibodies are uncommon.[10] Therefore, our patient's clinical profile does not match the typical features of DILE. However, DILE manifests not only lupus-like manifestations but also other sides of the spectrum, in which certain medications may induce SLE flares or unmask a clinically silent SLE.[10] In our patient, we propose a diagnosis of SJS/TEN and a preceding SLE exacerbation, presumably both caused by drugs. Other than medications, LE may have triggered SJS/TEN in our patient because LE is a risk factor for SJS/TEN.[1] Better understanding of the complex pathogenetic pathways involved in developing autoimmune diseases may help explain clinical phenotypic differences reported among patients, one of which was presented here.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ahu Yorulmaz;* ***Design:*** *Ahu Yorulmaz;* ***Control/Supervision:*** *Ahu Yorulmaz;* ***Data Collection and/or Processing:*** *Eylül Ceren Bal Bayazıtlı, Utku Orman;* ***Analysis and/or Interpretation:*** *Ahu Yorulmaz;* ***Literature Review:*** *Ahu Yorulmaz, Eylül Ceren Bal Bayazıtlı, Utku Orman, Emine Tamer, Huban Sibel Orhun;* ***Writing the Article:*** *Ahu Yorulmaz, Huban Sibel Orhun;* ***Critical Review:*** *Ahu Yorulmaz;* ***References and Fundings:*** *Ahu Yorulmaz;* ***Materials:*** *Eylül Ceren Bal Bayazıtlı, Utku Orman.*

REFERENCES

1. Truong K, Goldinger S, Kim J, Smith A, Fernandez-Peñas P. Toxic epidermal necrolysis-like lupus erythematosus: a condition to exclude in all patients with possible Stevens-Johnson syndrome/toxic epidermal necrolysis. J Eur Acad Dermatol Venereol. 2022;36(3):e218-e21. [Crossref] [PubMed]
2. Ziemer M, Kardaun SH, Liss Y, Mockenhaupt M. Stevens-Johnson syndrome and toxic epidermal necrolysis in patients with lupus erythematosus: a descriptive study of 17 cases from a national registry and review of the literature. Br J Dermatol. 2012;166(3):575-600. [Crossref] [PubMed]
3. Tankunakorn J, Sawatwarakul S, Vachiramon V, Chanprapaph K. Stevens-Johnson syndrome and toxic epidermal necrolysis-like lupus erythematosus. J Clin Rheumatol. 2019;25(5):224-31. [Crossref] [PubMed]
4. Rekvig OP. SLE classification criteria: Science-based icons or algorithmic distractions - an intellectually demanding dilemma. Front Immunol. 2022;13:1011591. [Crossref] [PubMed] [PMC]
5. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010;88(1):60-8. [Crossref] [PubMed]
6. He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. Curr Opin Rheumatol. 2018;30(5):490-7. [Crossref] [PubMed] [PMC]
7. Hofmann GA, Weber B. Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences. J Dtsch Dermatol Ges. 2021;19(1):19-29. [Crossref] [PubMed] [PMC]
8. Iarikov D, Wassel R, Farley J, Nambiar S. Adverse events associated with fosfomycin use: review of the literature and analyses of the FDA adverse event reporting system database. Infect Dis Ther. 2015;4(4):433-58. [Crossref] [PubMed] [PMC]
9. Blumenthal KG, Wickner PG, Lau JJ, Zhou L. Stevens-Johnson syndrome and toxic epidermal necrolysis: a cross-sectional analysis of patients in an integrated allergy repository of a large health care system. J Allergy Clin Immunol Pract. 2015;3(2):277-80.e1. [Crossref] [PubMed] [PMC]
10. Vaglio A, Grayson PC, Fenaroli P, Gianfreda D, Boccaletti V, Ghiggeri GM, et al. Drug-induced lupus: Traditional and new concepts. Autoimmun Rev. 2018;17(9):912-8. [Crossref] [PubMed]