

Stevens-Johnson syndrome triggered by cyclophosphamide: A rare clinical observation

Siklofosfamid ile tetiklenen Stevens-Johnson sendromu: Nadir bir klinik gözlem

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are rare, life-threatening mucocutaneous hypersensitivity reactions, predominantly triggered by medications such as antibiotics, antiepileptics, and non-steroidal anti-inflammatory drugs. Cyclophosphamide, though extensively used in autoimmune diseases and malignancies, is infrequently implicated in adverse reactions or complications. We report a rare case of SJS induced by cyclophosphamide in a patient with systemic lupus erythematosus and lupus nephritis. This case underscores the need for heightened clinical vigilance for rare but severe adverse drug reactions while managing patients with severe autoimmune diseases. Prompt recognition and withdrawal of the offending drug are essential for favorable outcomes.

Keywords: Stevens Johnson syndrome, cyclophosphamide, systemic lupus erythematosus, adverse drug reaction

Özet

Stevens-Johnson sendromu (SJS) ve toksik epidermal nekroliz, nadir görülen ve hayatı tehdit eden mukokutanöz aşırı duyarlılık reaksiyonlarıdır. Bu reaksiyonlar çoğunlukla antibiyotikler, antiepileptikler ve steroid olmayan anti-enflamatuvar ilaçlar gibi ilaçlar tarafından tetiklenir. Otoimmün hastalıklar ve malignitelerde yaygın olarak kullanılan siklofosfamid ise nadiren bu reaksiyonlara sebep olmaktadır. Biz, lupus nefritli sistemik lupus eritematozus hastasında siklofosfamid kaynaklı nadir bir SJS olgusunu sunuyoruz. Bu olgu, ağır otoimmün hastalıkların tedavisinde nadir fakat ciddi ilaç yan etkilerine karşı klinik dikkat ve farkındalığın artırılması gerektiğini vurgulamaktadır. Suçlu ilacın hızlı tanınması ve kesilmesi, olumlu sonuçlar için hayati öneme sahiptir.

Anahtar Kelimeler: Stevens-Johnson sendromu, siklofosfamid, sistemik lupus eritematozus, advers ilaç reaksiyonu

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe mucocutaneous hypersensitivity reactions, most frequently induced by medications. It is characterized by widespread epidermal necrosis, skin detachment, and involvement of multiple mucosal sites. Common culprits include antibiotics, antiepileptics, and non-steroidal anti-inflammatory drugs (NSAIDs).^[1] Early diagnosis and immediate discontinuation of the offending drug are critical. SJS is considered a medical emergency. Cyclophosphamide, an alkylating agent widely used in the treatment of autoimmune diseases

and malignancies, is not commonly associated with SJS. Reports of cyclophosphamide-induced SJS are exceedingly rare in the literature. We present a unique case of SJS in a patient with systemic lupus erythematosus (SLE) and lupus nephritis, caused by cyclophosphamide, underscoring the need for heightened clinical awareness even with less commonly implicated agents.

Case Presentation

A 23-year-old male with a history of vitiligo since childhood, initially presented with polyarthritis involving the small joints of the hands, wrists, knees, and ankles in a

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bilaterally symmetrical pattern, along with fever (recorded between 100-101 °F) and a skin rash over the malar eminences. These symptoms had been present for the past three months. On evaluation, he was found to have an elevated erythrocyte sedimentation rate (55 mm/hr), high C-reactive protein (23 mg/dL), negative rheumatoid factor, negative anti-cyclic citrullinated peptide antibody, and positive anti-nuclear antibody (by indirect immunofluorescence assay) (titer 1:160, homogeneous pattern). He was admitted for further evaluation. Subsequent investigations revealed high levels of anti-dsDNA, low complement levels (C3 and C4), and significant proteinuria on 24-hour urinary protein estimation (2.2 g/day). A kidney biopsy was performed, which revealed Class IV lupus nephritis with poor prognostic features, including crescents and fibrinoid necrosis (Figure 1). In view of these findings, he was treated with pulse methylprednisolone (500 mg daily for three consecutive days) along with the first dose of cyclophosphamide (15 mg/kg body weight). He was also started on hydroxychloroquine and angiotensin-converting enzyme inhibitors. The patient improved clinically with resolution of joint pain, subsidence of fever, and disappearance of the malar rash. He was discharged on oral prednisolone 60 mg daily and advised to continue monthly cyclophosphamide infusions. However, two weeks later, he developed generalized weakness, fatigue, malaise, fever, and new-onset skin rashes involving the face and trunk (Figures 2 and 3), which were associated with oral ulcerations. He was readmitted and re-evaluated for disease activity and other possible causes of the rash. Laboratory investigations revealed negative anti-dsDNA, normal C3 and C4 levels, and negative infectious work-up, including viral serologies for herpes and CMV. A dermatology consult was obtained, and a skin biopsy was performed. Histopathology revealed hydropic degeneration

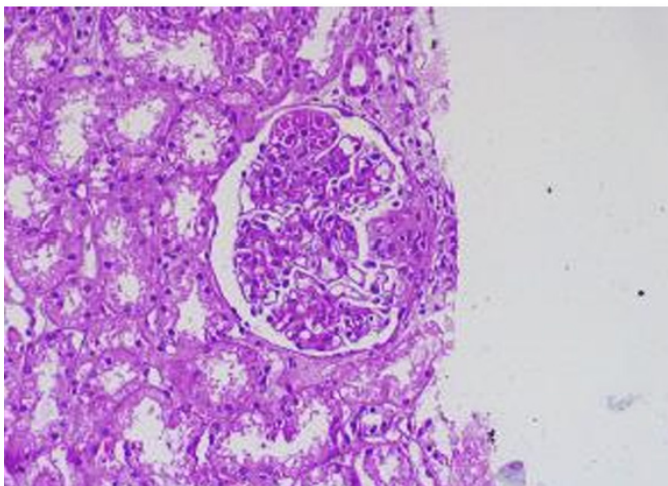


Figure 1. Kidney biopsy showing features of class IV lupus nephritis

of the basal layer with spongiosis, apoptotic keratinocytes, dermoepidermal clefting, epidermal necrosis, and moderate dermal inflammation with pigment incontinence. Direct immunofluorescence was negative for immunoglobulin (Ig)



Figure 2. Showing erythematous raised rashes with dusky centers, over anterior body surface with vitiligo patches



Figure 3. Showing erythematous macular raised rashes with dusky centers over head & neck area

M, IgG, C3, C1q, and IgA. These findings were consistent with SJS (Figure 4). The patient was again treated with pulse methylprednisolone (500 mg daily for three days) and intravenous Ig (IVIg) was planned. His condition improved, with resolution of fever and marked improvement in skin lesions. Cyclophosphamide was discontinued, and he was switched to Mycophenolate Mofetil and Tacrolimus. On follow-up visits, there was complete resolution of skin and mucosal lesions. At the three-month follow-up, oral steroids were tapered to 15 mg/day, and his proteinuria had decreased to 800 mg/24 hours. Currently, his disease remains in remission, and he has been advised to continue regular follow-up every 2-3 months.

Discussion

SJS/TEN is a rare, severe mucocutaneous reaction characterized by extensive necrosis and detachment of the epidermis. It is most commonly triggered by medications such as sulfonamides, anticonvulsants, and NSAIDs.^[2] While cyclophosphamide is widely used as an immunosuppressive agent in various autoimmune conditions, reports of cyclophosphamide-induced SJS are exceedingly rare.^[2] In the presented case, a 23-year-old male with SLE, and biopsy-proven Class IV lupus nephritis developed erythematous skin rashes following the administration of cyclophosphamide. The initial impression was that the skin rash was likely related to either active lupus disease or an infective cause, given the use of strong immunosuppressants, including cyclophosphamide and high-dose steroids. However, his infectious work-up was negative.^[3,4] To our surprise, skin biopsy findings were suggestive of SJS. A literature review revealed that cyclophosphamide-induced SJS is extremely rare. Jarret et al.^[5] reported SJS in a male patient with breast carcinoma who was treated with

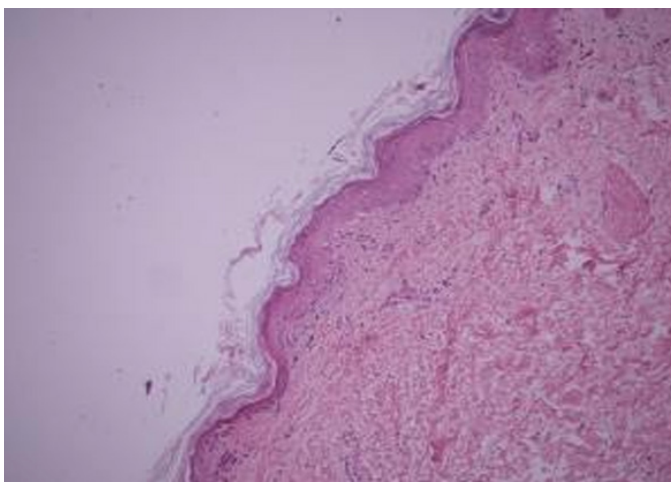


Figure 4. Showing hydropic degeneration of basal layer with spongiosis, dermoepidermal cleaving, apoptotic keratinocytes

docetaxel and cyclophosphamide, who developed SJS after the fourth chemotherapy cycle. Unfortunately, their patient died due to severe complications despite receiving steroids, IVIg, and supportive care. In contrast, our patient survived, possibly due to early recognition and discontinuation of the offending drug. Another case was reported by Chowdhury et al.^[6] in a patient with seronegative rheumatoid vasculitis who received cyclophosphamide. Assier-Bonnet et al.^[7] reported two cases of SJS linked to cyclophosphamide: a 55-year-old woman with Wegener's granulomatosis and a 53-year-old woman with polymyositis, both of whom developed severe skin eruptions that resolved after discontinuing cyclophosphamide, thereby confirming it as the likely cause. The uniqueness of our case lies in the relatively mild involvement of mucosal surfaces compared to extensive skin involvement, with no classical blistering or skin detachment. Additionally, there are case reports describing SLE itself presenting as SJS.^[8] However, in our patient, the resolution of skin rashes following the discontinuation of cyclophosphamide along with close follow-up strongly suggested a drug-induced reaction rather than primary lupus activity. In previous case reports, oral cyclophosphamide was used, whereas our case involved intravenous administration. Additionally, the mild mucosal involvement in our patient could have been easily mistaken for SLE manifestations. The management of SJS primarily involves immediate cessation of the offending agent and supportive care, which includes fluid and electrolyte management, meticulous wound care, and prevention of secondary infections. The use of systemic corticosteroids in SJS remains controversial. Some studies suggest that early administration may help halt disease progression and reduce mortality. In our case, the patient received pulse methylprednisolone therapy, which led to significant clinical improvement. As alternative immunosuppressive therapy, the patient was switched to mycophenolate mofetil and tacrolimus. These agents have demonstrated efficacy in inducing and maintaining remission in lupus nephritis while avoiding the risk of severe cutaneous adverse drug reactions.^[9] Biologic agents such as etanercept have also been reported as potential therapeutic options in severe SJS/TEN, particularly when initiated early in the disease course.^[10] However, these treatments require further validation through controlled clinical studies. Prompt recognition, immediate withdrawal of the offending drug, and early intervention are crucial to improving patient outcomes.^[11]

Conclusion

This case underscores the importance of vigilance for rare but potentially life-threatening adverse drug reactions,

such as SJS, in patients receiving cyclophosphamide. Clinicians should maintain a high index of suspicion when patients develop mucocutaneous symptoms following drug administration. Clinicians should remain vigilant for cutaneous adverse drug reactions, even with medications not commonly associated with SJS, to ensure timely diagnosis and management.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Concept: M.B., M.D., F.S., D.M.S., A.B., Design: M.B., M.D., F.S., D.M.S., A.B., Data Collection or Processing: M.B., M.D., F.S., D.M.S., A.B., Analysis or Interpretation: M.B., M.D., F.S., D.M.S., A.B., Literature Search: M.B., M.D., F.S., D.M.S., A.B., Writing: M.B., M.D., F.S., D.M.S., A.B.

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

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