Brief Report

Severe cutaneous adverse drug reactions: A search for the culprit in a retrospective study of 107 patients

Ghita Sqalli Houssini[1], Zakia Douhi[1], Meryem Soughi[1], Sara Elloudi[1], Hanane Baybay[1], Badreddine Moukafih[2], Marwa Elbaldi[3], Karima El Rhazi[3], Fatima Zahra Mernissi[1]

[1]Dermatology and Venereology Department, Hassan II University Hospital Center, Faculty of Medicine and Pharmacy, Sidi Mohamed Ben Abdellah University, Fez, Morocco, [2]Anatomy and Cytopathology Department, Hassan II University Hospital Center, Faculty of Medicine and Pharmacy, Sidi Mohamed Ben Abdellah University, Fez, Morocco, [3]Epidemiology and Public Health Laboratory, Faculty of Medicine and Pharmacy, Sidi Mohammed Ben Abdellah University, Fez, Morocco

Corresponding author: Ghita Sqalli Houssini, MD, E-mail: gsqallihoussini@gmail.com

ABSTRACT

Background: Severe drug eruptions, posing life-threatening risks, necessitate immediate discontinuation. This study (2014–2023) examined clinical profiles and prognoses in Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens–Johnson (SJS) syndrome, Toxic Epidermal Necrolysis (Lyell's syndrome), and Acute Generalized Exanthematous Pustulosis (AGEP). **Materials and Methods:** A retrospective analysis included hospitalized patients with severe drug reactions. **Results:** Implicated drugs: allopurinol (44.9%), neuroleptics (20.6%), antibiotics (12.1%), sulfasalazine (5.6%), and NSAIDs (5.6%). Allopurinol dominated in DRESS syndrome (51.4%), SJS (35.3%), Lyell's syndrome (45.5%). Neuroleptics caused SJS (35.3%), Lyell's syndrome (27.3%), and DRESS syndrome (18.1%). Antibiotics linked to AGEP (28.6%), SJS (17.6%), Lyell's syndrome (9.1%), and DRESS syndrome (9.7%). Sulfasalazine was associated with SJS (9.0%) and DRESS syndrome (6.9%), NSAIDs with AGEP (42.9%), and DRESS syndrome (4.2%). Significant correlations included sulfasalazine with hepatic impairment and allopurinol, neuroleptics, and antibiotics with renal failure. Mortality was 9.3%, primarily from allopurinol (60%), antibiotics (20%), and sulfasalazine (20%). **Conclusion**: Allopurinol and neuroleptics pose higher risks with significant correlations to severe complications. Haut du formulaire.

Key words: Drugs, Culprit, Allopurinol, DRESS syndrome, Stevens–Johnson syndrome, Lyell's syndrome

INTRODUCTION

Severe drug-induced skin reactions are acute idiosyncratic reactions, infrequent yet capable of compromising the prognosis and constituting a diagnostic and therapeutic emergency. Hence, there is a legal obligation to report them to pharmacovigilance authorities. Severe drug-induced skin reactions encompass Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Stevens–Johnson syndrome (SJS), Toxic Epidermal Necrolysis (Lyell's syndrome), and Acute Generalized Exanthematous Pustulosis. Diagnosis relies on a combination of clinical, biological, histological, and chronological evidence. Treatment is not well standardized, yet immediate cessation of the suspected drug is the crucial step in both immediate and subsequent therapeutic management. All drugs may be implicated, with the most common ones being antiepileptics, allopurinol, nonsteroidal anti-inflammatory drugs (NSAIDs), and antibacterial sulfonamides [1,2]. Our study aimed to investigate the drugs most frequently associated with severe drug-induced skin reactions by analyzing the clinical profile and associated prognosis.

MATERIALS AND METHODS

We conducted a retrospective, descriptive, and analytical study at the Dermatology Department of

How to cite this article: Houssini GS, Douhi Z, Soughi M, Elloudi S, Baybay H, Moukafih B, Elbaldi M, El Rhazi K, Mernissi FZ. Severe cutaneous adverse drug reactions: A search for the culprit in a retrospective study of 107 patients. Our Dermatol Online. 2025;16(1):43-47.

Submission: 10.01.2024; **Acceptance:** 28.02.2024
DOI: 10.7241/ourd.20251.6

© Our Dermatol Online 1.2025

CHU HASSAN II in Fez over the period from 2014 to 2023.

All patients hospitalized for severe drug-induced skin reactions (DRESS syndrome, SJS/Lyell's syndrome, AGEP) were included, and the diagnosis was based on clinical, biological, histological, and chronological criteria, referring to data provided by the pharmacovigilance laboratory. The RegiSCAR score was calculated for cases of DRESS syndrome.

Drug-induced vasculitis and angioedema cases were excluded.

Data analysis was performed with SPSS software, version 26, employing the chi-squared test and Fisher's test to investigate various correlations. A p value was considered significant if it was less than 0.05 ($p < 0.05$).

RESULTS

In our study, a total of 107 patients were included, comprising 34.6% of men and 65.4% of women, with an average age of 53.48 years. As for the medical history, 20.6% had diabetes, 6.5% had renal insufficiency, 34% had cardiovascular diseases (heart failure, hypertension, ischemia), and 2.8% had a neoplasm.

Hospitalization involved 72 cases of DRESS syndrome (67.3%), 17 cases of Stevens–Johnson syndrome (SJS) (15.9%), 11 cases of Lyell's syndrome (10.3%), and 7 cases of acute generalized exanthematous pustulosis (AGEP) (6.5%).

The most implicated drugs, in descending order, were allopurinol (44.9%), neuroleptics (20.6%), antibiotics (12.1%), sulfasalazine, and non-steroidal anti-inflammatory drugs (NSAIDs) (5.6% each) (Fig. 1).

Allopurinol caused 51.4% of DRESS syndrome cases, 45.5% of Lyell's syndrome cases, and 35.3% of SJS cases, with no cases of AGEP. Neuroleptics resulted in 35.3% of SJS cases, 27.3% of Lyell's syndrome cases, and 18.1% of DRESS cases, with no cases of AGEP. Antibiotics were responsible for 28.6% of AGEP cases, 17.6% of SJS cases, 9.1% of Lyell's syndrome cases, and 9.7% of DRESS syndrome cases. Sulfasalazine caused 9.1% of SJS cases and 6.9% of DRESS syndrome cases, with no cases of SJS or AGEP. NSAIDs led to 42.9% of AGEP cases, 4.2% of DRESS syndrome cases, with no cases of Lyell's syndrome or SJS. Fig. 2 summarizes the different forms of severe cutaneous adverse drug reactions based on each medication. No statistically significant correlation was found between the type of drug eruption and the implicated medication.

Systemic involvement included 39.3% of hepatic, 47.7% of renal, and 64.5% of eosinophilia cases. Allopurinol, neuroleptics, antibiotics, sulfasalazine, and NSAIDs caused hepatic involvement in 50%, 16.7%, 9.5%, 11.9%, and 2.4%, respectively. Similarly, they caused renal involvement in 70.6%, 11.8%, 3.9%, 3.9%, and 3.9%, respectively. A statistically significant association was found between renal involvement and allopurinol, neuroleptics, and antibiotics. Another significant correlation was noted between sulfasalazine and hepatic involvement. Regarding eosinophilia, allopurinol had the highest contribution (57%), followed by neuroleptics (21%), antibiotics (14%), sulfasalazine (5%), and NSAIDs (3%), yet no significant correlation was established. Table 1 summarizes all systemic involvements correlated with the implicated drugs.

Out of the total sample, there were 10 deaths (9.3%), with 6 cases in DRESS syndrome (8.3%) and 4 in Lyell's syndrome (6.4%), and none in AGEP or SJS. Allopurinol was responsible for 60% of deaths, while sulfasalazine and antibiotics each led to 20% of mortalities.

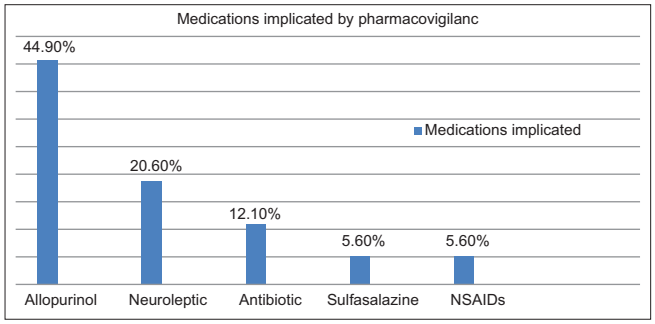

Figure 1: Various implicated medications.

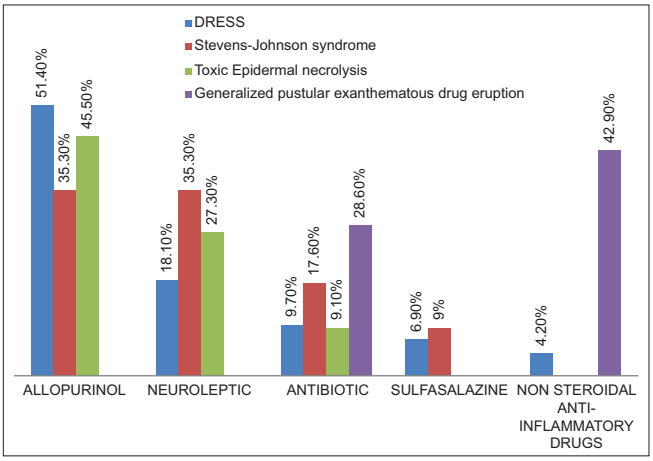

Figure 2: Type of drug eruption and associated medication.

Table 1: Systemic involvements and implicated medications

Culprit	Liver involvement	*p* value	Kidney involvement	*p* value	Eosinophilia	*p* value
Allopurinol	21 (50%)	0.39	36 (70.6%)	0.001*	35 (50.7%)	0.1
Neuroleptic	7 (16.7%)	0.423	6 (11.8%)	0.032*	13 (18.8%)	0.553
Antibiotic	4 (9.5%)	0.504	2 (3.9%)	0.013*	9 (13%)	0.768
Sulfasalazine	5 (11.9%)	0.033*	2 (3.9%)	0.681	3 (4.3%)	0.664
NSAIDs (non-steroidal anti-inflammatory drugs)	1 (2.4%)	0.4	2 (3.9%)	0.681	2 (2.9%)	0.183

*: $p < 0.05$ = significant

Follow-up revealed 3.7% of systemic sequelae, all dysthyroidies, and 30.8% of cutaneous-mucous sequelae, predominantly post-inflammatory hyperpigmentation (72.7%) (Fig. 3a), nail abnormalities (9%) (Fig. 3b), cutaneous xerosis (40.4%), genital synechiae (12%) (Fig. 3c), and ocular synechiae (9%) (Fig. 3d). Allopurinol was accountable for all systemic sequelae and 50% of cutaneous-mucous sequelae, while neuroleptics, NSAIDs, and sulfasalazine caused 27.27%, 6%, and 3% of cutaneous-mucous sequelae, respectively. No significant correlation was established between mortality or sequelae and the various implicated drugs.

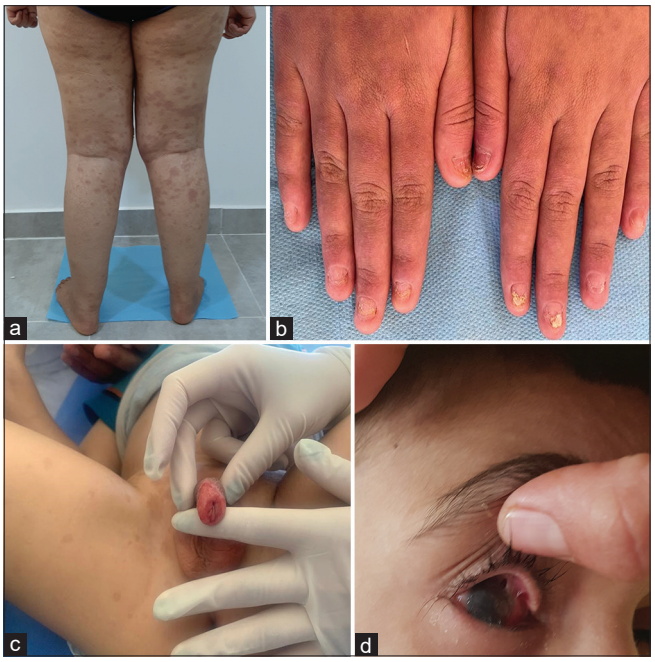

Figure 3: Clinical images of cutaneous and mucosal sequelae: a) post-inflammatory hyperpigmentation following DRESS syndrome, b) anonychia following Lyell's syndrome, c) genital synechia following Stevens–Johnson syndrome, d) ocular synechiae following Lyell's syndrome.

DISCUSSION

The term *toxidermia* encompasses all cutaneous and mucosal adverse effects following the administration of a drug internally [3]. These are unpredictable skin reactions that are not dose-dependent; they do not depend on the conventional dose of the drug yet rather on the individual and their personal constitution and the drug itself [4]. Thus, they are defined as hypersensitivity reactions, whether immunologic or not, ranging from a simple benign rash to more severe conditions such as DRESS syndrome, Stevens–Johnson syndrome, Lyell's syndrome, and finally PEAG. Although rare, severe toxidermias occur in 2% of hospitalized patients [4], the severity of systemic involvement necessitates the physician to, firstly, diagnose them rapidly, secondly, identify the causative drug for immediate cessation to improve the patient's prognosis; and finally, know how to direct the patient to the appropriate department, either to intensive care for extensive toxic epidermal necrolysis or to a dermatology service [5]. Early discontinuation of the suspected drug and reporting to pharmacovigilance units not only aids in diagnosis yet also improves immediate and long-term prognosis, as demonstrated, at least for SJS and Lyell's syndrome [6].

A multitude of drugs may be implicated, with most studies agreeing that antiepileptic drugs, especially carbamazepine, phenytoin, antibiotics, anti-inflammatories, and allopurinol, are the leading culprits [1,4]. Our findings align with the literature, identifying the same implicated molecules, although allopurinol is at the forefront. This may be explained by our predominantly elderly population with cardiovascular and renal histories, leading to more frequent allopurinol prescriptions by cardiologists, nephrologists, and family physicians for such patients.

However, each type of toxidermia is associated with a specific drug. In our study, we found that neuroleptics were mainly responsible for SJS and Lyell's syndrome, followed by DRESS syndrome, aligning with work by Yan et al. on severe toxidermias from neuroleptics in the Asian population [7]. They demonstrated that aromatic antiepileptics such as carbamazepine, lamotrigine, and phenytoin were primarily responsible for SJS and Lyell's syndrome and secondarily for DRESS syndrome. The carbamazepine is also identified as the main cause of DRESS syndrome in the European Register of Severe Cutaneous Adverse Reactions (RegiSCAR) [8]. Other antiepileptic drugs responsible for severe

toxidermias are phenytoin, lamotrigine, oxcarbazepine, levetiracetam, and topiramate [9].

The risk of developing such reactions depends on various factors, including genetic predispositions and non-genetic variables. The frequency and nature of these reactions vary significantly among ethnic groups and geographical regions. Several studies have established a close link between HLA (human leukocyte antigen) alleles and drug-induced skin reactions [1]. For instance, in the European and Japanese populations, the HLA-A31.01 allele is specifically associated with carbamazepine-related adverse effects, especially for DRESS syndrome [1,10]. However, the HLA-B15:02 allele is also implicated in toxic epidermal necrolysis reactions (SJS and Lyell's syndrome) for carbamazepine and other aromatic antiepileptics in the Chinese population [1]. This genetic and ethnic variability could explain the difference in results.

In our series, allopurinol caused 51.4% of DRESS syndrome cases, 45.5% of Lyell's syndrome cases, and 35.3% of SJS cases, with no cases of PEAG. This aligned with findings by Park et al. on the clinical characteristics and prognosis of allopurinol-induced toxidermias, where DRESS syndrome, followed by SJS and Lyell's syndrome, were the most reported, with no cases of PEAG [11]. They also showed that allopurinol led to more pronounced eosinophilia compared to other drugs, which was consistent with our results. Although the majority of allopurinol users tolerate it, some may develop hypersensitivity reactions. Approx. 1% to 5% of allopurinol users experience minor side effects [12]. Severe toxidermias related to allopurinol are observed in about 0.4% of new users, with a high mortality rate ranging from 9% to 32% [13-15]. These patients may die due to multi-systemic involvement or infection. The increasing prevalence of gout worldwide, the affordability of the drug, and its widespread prescription by many specialists explain the growing prevalence of allopurinol-induced toxidermias. This aligned with our results; allopurinol was the most frequently reported agent in our study, causing the most hepatic and renal systemic involvement, with the highest mortality rate and systemic and cutaneous/mucosal sequelae.

As for PEAG, long considered a variant of psoriasis, it is mostly caused by several drugs such as antibiotics (beta-lactams, aminopenicillins, sulfonamides, quinolones), as well as terbinafine, fluconazole, diltiazem, and hydroxychloroquine. It may also be secondary to the consumption of certain plants or insect venom [1]. Its prognosis is generally favorable, with reduced mortality [4]. To our knowledge, our study is the first to shed light on the association between the suspected drug and internal organ involvement, with significant results for sulfasalazine and hepatic involvement and for allopurinol, neuroleptics, antibiotics, and renal involvement. The implication of sulfasalazine as a sulfonamide in severe toxidermias has been reported [16,17], as well as the hepatotoxicity it may cause [18]. Finally, our results align with other studies on the Moroccan population, showing that in DRESS syndrome [19] and in the spectrum of SJS and Lyell's syndrome [20], allopurinol was the most incriminated drug, followed by neuroleptics and antibiotics, with the liver and kidney being the two most affected organs.

Regarding prognosis, the mortality rate was higher for Lyell's syndrome, followed by DRESS, which was consistent with the literature [1]. Allopurinol, sulfasalazine, and antibiotics were the leading causes of death, in order of frequency. We attribute this to the fact that allopurinol induced the most severe toxidermias and systemic involvement, while sulfasalazine led to more SJS cases and was significantly associated with hepatic involvement. Finally, there were no deaths from neuroleptics in our series, possibly due to the rapid discontinuation of the drug, which is often easily reported by the family and the patient themselves, a further indication of the importance of promptly seeking and stopping the suspected drug. As for the sequelae, allopurinol was the medication most associated with sequelae, followed by neuroleptics. This is due to the fact that these two medications caused the most cases of SJS and Lyell's syndrome and DRESS syndrome. It is noteworthy that DRESS syndrome is a chronic disease with long-term sequelae, whether cutaneous or systemic, such as thyroid disorders, diabetes, alopecia, and other systemic diseases [21]. Since, in our series, DRESS syndrome was most commonly associated with allopurinol, this explains why all systemic sequelae and the majority of cutaneous and mucosal sequelae are attributed to it. Finally, neuroleptics are mainly responsible for toxic epidermal necrolysis. This serious condition, considered an extensive and severe burn of the skin, explains its involvement in cutaneous and mucosal sequelae, including genital and ocular involvement [22].

CONCLUSION

Allopurinol, neuroleptics, antibiotics, and sulfasalazine were the most implicated drugs in our study. The

clinical profile we observed was as follows: Allopurinol and neuroleptics were mainly associated with DRESS syndrome and SJS/Lyell's syndrome, while antibiotics were responsible for conditions ranging in severity from PEAG to SJS. Allopurinol, neuroleptics, antibiotics, and sulfasalazine were linked to systemic involvement. In terms of prognosis, Allopurinol was associated with systemic and cutaneous-mucosal sequelae and significant mortality. On the other hand, neuroleptics did not result in any deaths due to their rapid identification as the suspected drug and immediate discontinuation.

Given the strong association with Allopurinol, it would be prudent to carefully consider the merits and drawbacks before prescribing it, while raising awareness among cardiologists, nephrologists, rheumatologists, and general practitioners.

According to some authors, initiating treatment with a dose not exceeding 100 mg could be an alternative to mitigate the severity of cutaneous reactions to Allopurinol. Further in-depth studies in this regard are necessary.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

REFERENCES

1. Owen CE, Jones JM. Recognition and management of severe cutaneous adverse drug reactions (including drug reaction with eosinophilia and systemic symptoms, Stevens–Johnson syndrome, and toxic epidermal necrolysis). Med Clin North Am. 2021;105:577-97.
2. Antoine G, Saskia IHO, Olivier C, Nicolas P. Severe cutaneous adverse drug reaction in intensive care. Méd Intensive Réa. 2023;32:159-172
3. Bourrain JL. Toxidermies. Ann Dermatol Vénéréol. 2019;146:740-55.
4. Zhang J, Lei Z, Xu C, Zhao J, Kang X. Current perspectives on severe drug eruption. Clin Rev Allergy Immunol. 2021;61:282-98.
5. Ingen-Housz-Oro S, Duong TA, de Prost N, Colin A, Fardet L, Lebrun-Vignes B, et al. [Treatment of severe cutaneous adverse drug reactions]. Ann Dermatol Venereol. 2018;145:454-64.
6. Garcia-Doval I, Le Cleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: Does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol. 2000;136:323-7.
7. Yang CY, Dao RL, Lee TJ, Lu CW, Yang CH, Hung SI, et al. Severe cutaneous adverse reactions to antiepileptic drugs in Asians. Neurology. 2011;77:2025-33.
8. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: A literature review. Am J Med. 2011;124:588-97.
9. Chung SJ, Ahn KM, Oh JH, Shim JS, Park HW. Incidence rates of severe cutaneous adverse reactions due to antiseizure medication: A nationwide study using health claims data in Korea. Epilepsia. 2021;62:250-7.
10. Borchers AT, Lee JL, Naguwa SM, Cheema GS, Gershwin ME. Stevens–Johnson syndrome and toxic epidermal necrolysis. Autoimmun Rev. 2008;7:598-605.
11. Park HJ, Yun J, Kang DY, Park JW, Koh YI, Kim S, et al. Unique clinical characteristics and prognosis of allopurinol-induced severe cutaneous adverse reactions. J Allergy Clin Immunol Pract. 2019;7:2739-2749.e3.
12. McInnes GT, Lawson DH, Jick H. Acute adverse reactions attributed to allopurinol in hospitalised patients. Ann Rheum Dis. 1981;40:245-9.
13. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, et al. Allopurinol is the most common cause of Stevens–Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol. 2008;58:25-32.
14. Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum. 1986;29:82-7.
15. Ramasamy SN, Korb-Wells CS, Kannangara DR, Smith MW, Wang N, Roberts DM, et al. Allopurinol hypersensitivity: A systematic review of all published cases. Drug Saf. 2013;36:953-80.
16. Kanabaj K, Jenerowicz D, Jankowska L, Żaba Z. DRESS syndrome: A dermatological emergency: Sulfasalazine-related acute drug reaction case report. Heliyon. 2023;9:e20021.
17. Bialynicki-Birula R, Cisoń W, Krefft-Trzciniecka H, Cisoń H. Acute generalized exanthematous pustulosis caused by sulfasalazine. Our Dermatol Online. 2024;15:71-4.
18. Jennings PE, Blandford RL, Rosenthal FD. Acute sulphasalazine hepatotoxicity. Postgrad Med J. 1986;62:305-6.
19. Mehsas Z, Boubnane I, Sektaoui S, Meziane M, Ismaili N, Benzekri L, et al. DRESS syndrome: A descriptive series of 62 cases. Our Dermatol Online. 2023;14:268-73.
20. Chagraoui H, Hali F, Meftah A, Filali H, Chiheb S. Aspects pharmaco-cliniques, thérapeutiques et évolutifs du spectre Stevens-Johnson et Lyell (série de 27 cas). Rev Fr Allergol. 2023;63:103250.
21. Bensaid B, Jullien D. Évaluation des sequelles dans les DRESS : une série de 79 patients. Ann Dermatol Venereol. 2020;147:A86.
22. Lee HY, Walsh SA, Creamer D. Long-term complications of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN): The spectrum of chronic problems in patients who survive an episode of SJS/TEN necessitates multidisciplinary follow-up. Br J Dermatol. 2017;177:924-35.
23. Stamp LK, Chapman PT. Allopurinol hypersensitivity: Pathogenesis and prevention. Best Pract Res Clin Rheumatol. 2020;34:101501.

Copyright by Ghita Sqalli Houssini, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Source of Support: This article has no funding source.

Conflict of Interest: The authors have no conflict of interest to declare.