A Rare Case of Acne Medication-Induced Drug Reaction With Eosinophilia and Systemic Symptoms

Benjamin L. Hamel, MD; Sadie F. Mason, MD; Alina G. Burek; Kristen E. Holland, MD

ABSTRACT

Introduction: Acne vulgaris is the most common skin condition in late adolescence and frequently requires systemic treatment with antibiotics or androgen receptor blockers in moderate-to-severe cases.

Case Presentation: We report the case of a 17-year-old adolescent female with new onset fever, headache, and pruritic rash 1 month after she started doxycycline and spironolactone for the treatment of acne vulgaris. Later, she developed eosinophilia and transaminitis. Infectious workup was negative.

Discussion: This presentation was consistent with a definite case of drug reaction and eosinophilia with systemic symptoms (DRESS). DRESS is a severe, systemic hypersensitivity drug reaction that typically occurs 2 to 8 weeks following exposure to the offending medication.

Conclusion: Although doxycycline and spironolactone are uncommon triggers of DRESS, they are common medications used to treat acne, and clinicians should be aware of this potential complication when counseling patients, especially adolescents.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a life-threatening, systemic hypersensitivity drug reaction that typically occurs 2 to 8 weeks following exposure to the offending medication. The pathophysiology of DRESS is not completely understood but is thought to involve the reactivation of herpes viruses (eg, human herpesvirus 6 [HHV 6], human herpesvirus 7 [HHV7], Epstein-Barr virus, and cytomegalovirus) and subsequent immune response by the body.[1] The constellation of symptoms that occur with DRESS has made it a somewhat difficult diagnosis, although proposed diagnostic criteria have been developed based on clinical and laboratory features. One scoring system that is commonly used to establish the diagnosis is the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) criteria. The RegiSCAR criteria are shown in the Table and include the following characteristics: (1) fever (≥ 38.5 °C), (2) enlarged lymph nodes, (3) eosinophilia (> 700/μL or > 10%), (4) atypical lymphocytes, (5) skin rash, (6) internal organ involvement, and (7) resolution in ≥ 15 days. Patients are classified by possible (score 2-3), probable (score 4-5), definite (score ≥ 6), or no case (score < 2) based on how many of the criteria they satisfy.[2]

The authors present the unusual case of an adolescent girl diagnosed with DRESS after starting treatment with doxycycline and spironolactone for acne vulgaris.

CASE REPORT

A 17-year-old female presented with new onset fever, headache, and pruritic rash for 2 days. Past medical history was significant for acne vulgaris treated for the last month with twice daily doxycycline 100 mg and spironolactone 25 mg. She was not taking any other medications regularly at the time and reported no recent exposure to nonsteroidal anti-inflammatory drugs (NSAID), though these were used after her initial presentation to treat her

• • •

Author Affiliations: Department of Pediatrics, Medical College of Wisconsin (MCW), Milwaukee, Wisconsin (Hamel, Mason, Burek); Children's Wisconsin, Milwaukee, Wisconsin (Mason, Burek, Holland); Department of Dermatology, Medical College of Wisconsin, Milwaukee, Wisconsin (Holland).

Corresponding Author: Benjamin L. Hamel, MD, Children's Hospital of Wisconsin, Children's Corporate Center Suite 730, Milwaukee, WI 53226; phone 651.324.1383; email benjaminlhamel@gmail.com; ORCID ID 0000-0001-8086-3428

Published online Aug 3, 2022.

fever. Physical exam during the first 24 hours was notable for fever up to 39.4 °C, tachycardia up to 130 beats per minute, and blood pressure as low as 83/51 mmHg. She had facial edema and palatal petechiae. Lymphadenopathy was not appreciated. On skin exam, she had confluent blanchable erythema of the trunk and face, with discrete and confluent macules, papules, and atypical targetoid papules over the extremities. Violaceous, nonblanching macules coalescing into patches also were noted on the proximal extremities (Figure 1A).

Laboratory testing was significant for transaminitis and leukocytosis with neutrophilia (Figures 2A and 2B). Her infectious workup, which included a respiratory pathogen panel, was negative for group A streptococci, Epstein-Barr virus, cytomegalovirus, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, HHV-6, and COVID-19. Cerebrospinal fluid and blood cultures were negative. Skin biopsy of the right thigh demonstrated mild spongiosis with focal interface dermatitis and mixed perivascular infiltrate without features of vasculitis (Figure 3). Direct immunofluorescence findings were nonspecific without fibrin/IgA/IgG deposition.

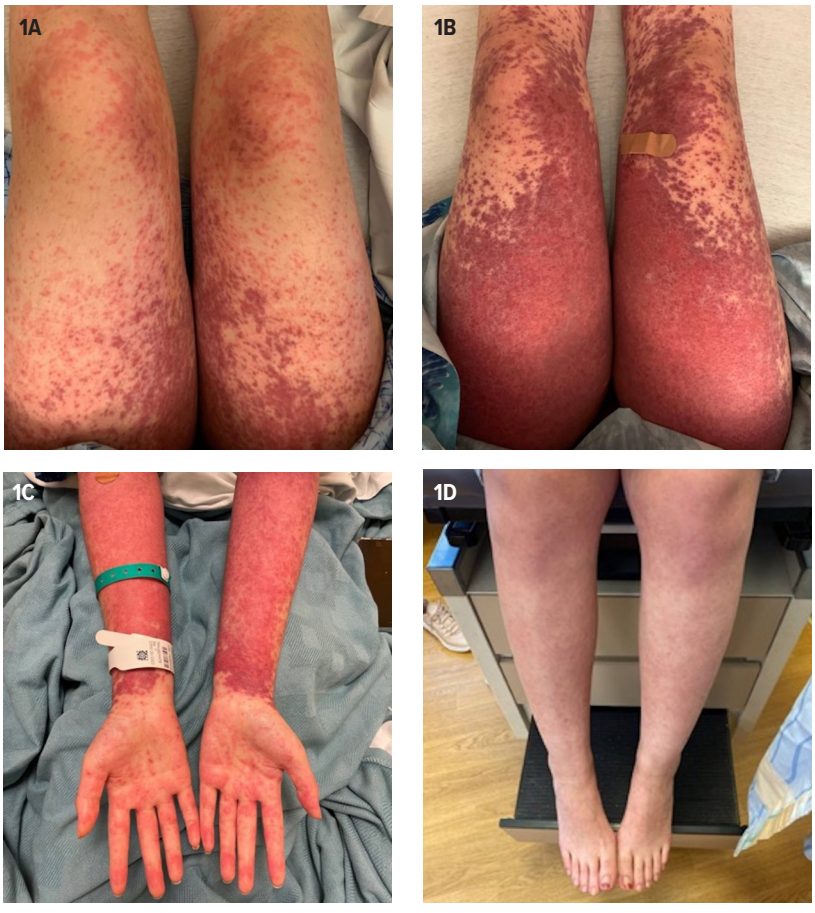
The day after presentation, the patients was started on topical corticosteroids (triamcinolone 0.1% and clobetasol 0.05%) and oral prednisone 1 mg/kg/day for suspected DRESS. Over the next 2 days, her systemic symptoms (fever, tachycardia, and hypotension) improved, but she developed increasing cutaneous involvement (Figure 1B and 1C) and worsening facial edema. Eosinophilia developed on the third day of hospitalization. In light of her negative infectious workup, development of eosinophilia, and skin pathology, the definitive diagnosis of DRESS was made. She was discharged home on a 6-week prednisone taper. At 1-month follow-up, she demonstrated near complete resolution of the skin eruption (Figure 1D) and normalization of her transaminitis (Figure 2A).

Table. European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) Criteria for DRESS Syndrome

Criterion	Score			Notes
	-1	0	+1	
Fever ≥ 38.5 °C	N/U	Y		
Enlarged lymph nodes		N/U	Y	>1 cm and ≥ 2 different areas
Eosinophilia ≥ 0.7 x 10^9/L or ≥ 10% if WBC ≤ 4 x 10^9		N/U	Y	Score 2, when ≥ 1.5 x 10^9 or ≥ 20% if WBC ≤ 4 x 10^9
Atypical lymphocytosis		N/U	Y	
Skin rash				Rash suggesting DRESS: ≥ 2 symptoms: purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Extent > 50% of body surface area		N/U	Y	
Rash suggesting DRESS	N	U	Y	
Skin biopsy suggestion DRESS	N	Y/U		
Organ involvement		N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution ≥ 15 days	N/U	Y		
Excluding other causes		N/U	Y	Score 1 if 3 tests of the following were performed and all were negative: HAV, HBV, HCV, mycoplasma, chlamydia, ANA, blood culture

Abbreviations: DRESS: drug reaction with eosinophilia and systemic symptoms; N, no; U, unknown; Y, yes; WBC, white blood cell count; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; ANA, antinuclear-antibody.

Figure 1. Progression of Patient's Rash During Hospitalization and Follow-up



Lower extremity skin changes with violaceous, nonblanching macules coalescing into patches at presentation (1A) and 2 days after presentation (1B); upper extremity changes with dark violet purpuric patches with thin papules and plaques in some areas along with pink macules and papules on palmar hands 2 days after presentation (1C); resolution of violaceous patches and significant interval decrease in redness in lower extremities at 1-month follow-up (1D).

Published online Aug 3, 2022.

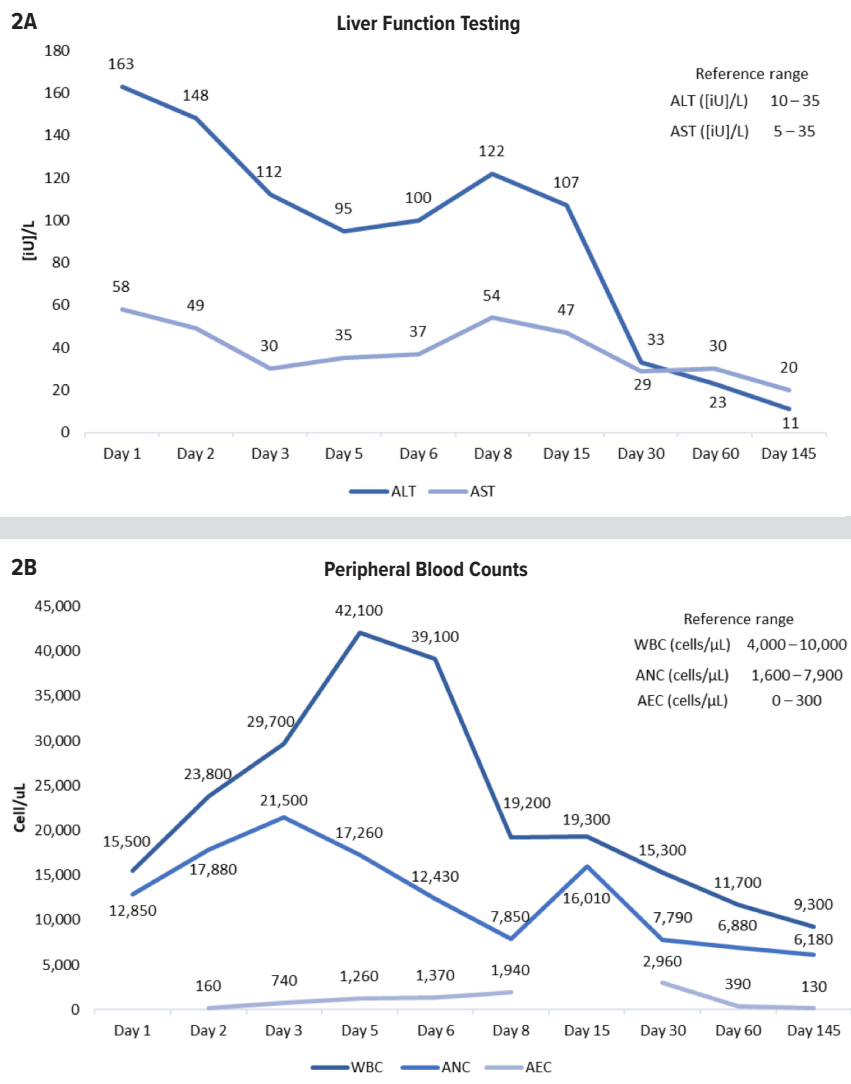
DISCUSSION

Our patient, who began spironolactone and doxycycline for acne vulgaris a month prior to presentation, satisfied the RegiSCAR criteria with a score of 6 (fever ≥38.5 °C, eosinophilia, skin rash >50% body surface area and suggestive of DRESS, transaminitis, other potential causes excluded), which is classified as a definite case. While many medications have been reported in association with DRESS, the most commonly reported are antibiotics (such as minocycline, sulfonamides, vancomycin, and cephalosporins), NSAIDs, and antiepileptic drugs.[2] Doxycycline and spironolactone are uncommon triggers of DRESS that have been infrequently described in the literature.[3,4] Skin patch testing is a safe diagnostic test for determining the causative medication in DRESS; however, while it has high specificity, sensitivity varies widely, yielding positive tests in only one-third to one-half of DRESS patients.[5] This testing was not pursued in our patient given the extent of her rash.

A skin biopsy should be obtained in cases of suspected DRESS for histopathologic examination, as the cutaneous findings (maculopapular eruption with progression to a coalescing erythema) are nonspecific. Histology can demonstrate interface dermatitis with vacuolization, spongiosis, keratinocyte damage, perivascular lymphocytic infiltration, red blood cell extravasation, and vessel wall destruction.[6] Lymphocytic or leukocytoclastic vasculitis is not seen, but nuclear debris may be observed.[7]

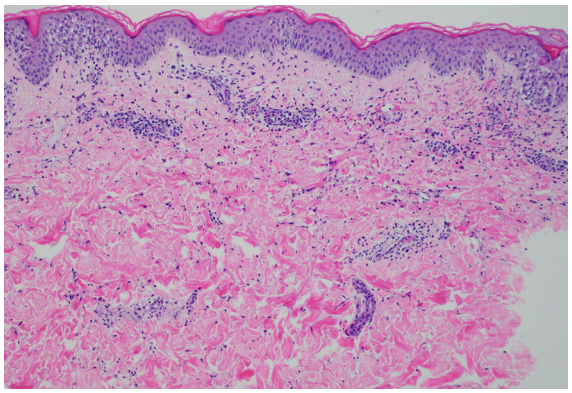
The most important proximal step in the management of DRESS is immediate withdrawal of the inciting agent(s). In our patient, the doxycycline and spironolactone were stopped by the patient the morning her symptoms first started (2 days prior to initial presentation). In mild cases of DRESS (limited or no organ involvement), supportive care only and topical corticosteroids may be appropriate. For more severe cases (ie, involvement of 1 or more organs), systemic corticosteroids are considered the mainstay of treatment. Prednisolone or an equivalent of 0.5-1.0 mg/kg/day with a 2- to 3-month taper has been shown to be an effective treatment.[8] The use of systemic corticosteroids has been associated with a greater risk of infectious complications and increased incidence of flareups.[9] Flareups usually manifest as cutaneous eruptions but

Figure 2. Line Graphs Showing Trends of Selected Laboratory Values Over Time



Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; ANC, absolute neutrophil count; AEC, absolute eosinophil count.

Figure 3. Histological Image of Right Thigh Biopsy Showing Mild Spongiosis With Focal Interface Dermatitis With Leukocytoclasia and Red Blood Cell Extravasation Without Appreciation of Vasculitis



Hematoxylin and eosin; original magnification x10.

Published online Aug 3, 2022.

may also include eosinophilia or transaminitis,[10] and such recurrences have been observed in up to 25% of DRESS cases, regardless of treatment.[11] It is important to note that development of autoimmune sequelae such as lupus erythematous and autoimmune thyroiditis, as well as type 1 diabetes mellitus, autoimmune hemolytic anemia, and alopecia areata, have been observed in DRESS survivors, usually occurring more than 6 months following the acute infection phase.[11]

This case highlights a serious complication of systemic acne vulgaris treatment. Acne vulgaris is estimated to affect approximately 85% of teens and young adults age 12 to 25 years and is one of the most prevalent skin conditions in the United States.[12] Both doxycycline and spironolactone are frequently prescribed in the teenage population for treatment of medium-to-severe cases.[13,14] Clinicians need to understand the potential complications associated with systemic treatment of acne vulgaris in teens and also consider DRESS as a possible diagnosis in cases of acute onset fever and rash developing weeks after the initiation of those medications.

CONCLUSIONS

Patients who have developed DRESS should be counseled to avoid confirmed or suspected medications given the risk of recurrent or more severe DRESS with re-exposure. In patients with more than 1 suspected agent, skin patch testing may be helpful in providing guidance, particularly if therapeutic alternatives are limited. Patients also should be monitored for the development of autoimmune sequelae, which can occur months after recovery.

Acknowledgements: Parental consent for publication of patient images was obtained in writing.

Funding/Support: None declared.

Conflict of Interest Disclosures: Dr Holland reported serving as a principal investigator on clinical trials for Sanofi, AbbVie, Amgen, Incyte Corp, and Pfizer. Fees for this contracted research were paid to the institution. No other disclosures were reported.

REFERENCES

1. Descamps V, Ranger-Rogez S. DRESS syndrome. *Joint Bone Spine*. 2014;81(1):15-21. doi:10.1016/j.jbspin.2013.05.002

2. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol*. 2013;169(5):1071-1080. doi:10.1111/bjd.12501

3. Sharifzadeh S, Mohammadpour AH, Tavanaee A, Elyasi S. Antibacterial antibiotic-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a literature review. *Eur J Clin Pharmacol. 2021;77(3):275-289. doi:10.1007/s00228-020-03005-9*

4. Bains A, Rajagopal SV, Rao M. DRESS syndrome secondary to spironolactone with atypical presentation. *Indian Dermatol Online J*. 2020;11(6):1022-1023. doi:10.4103/idoj.IDOJ_279_20

5. Gonçalo M. Usefulness of cutaneous provocation tests to study drugs responsible for cutaneous adverse drug reactions. *Curr Treat Options Allergy.* 2019;6(1):112-124. doi:10.1007/s40521-019-0198-4

6. Bouiller K, Audia S, Devilliers H, et al. Etiologies and prognostic factors of leukocytoclastic vasculitis with skin involvement: a retrospective study in 112 patients. *Medicine (Baltimore).* 2016;95(28):e4238. doi:10.1097/MD.0000000000004238

7. Ortonne N, Valeyrie-Allanore L, Bastuji-Garin S, et al. Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: a morphological and phenotypical study. *Br J Dermatol.* 2015;173(1):50-58. doi:10.1111/bjd.13683

8. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system. *Int J Mol Sci.* 2017;18(6):1243. doi:10.3390/ijms18061243

9. Funck-Brentano E, Duong TA, Bouvresse S, et al. Therapeutic management of DRESS: a retrospective study of 38 cases. J *Am Acad Dermatol.* 2015;72(2):246-252. doi:10.1016/j.jaad.2014.10.032

10. Picard D, Vellar M, Janela B, Roussel A, Joly P, Musette P. Recurrence of drug-induced reactions in DRESS patients. J *Eur Acad Dermatol Venereol*. 2015;29(4):801-804. doi:10.1111/jdv.12419

11. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *J Am Acad Dermatol.* 2013;68(3):459-465. doi:10.1016/j.jaad.2012.08.009

12. Rathi SK. Acne vulgaris treatment: the current scenario. *Indian J Dermatol.* 2011;56(1):7-13. doi:10.4103/0019-5154.77543

13. Poinas A, Lemoigne M, Le Naour S, et al. FASCE, the benefit of spironolactone for treating acne in women: study protocol for a randomized double-blind trial. *Trials*. 2020;21(1):571. doi:10.1186/s13063-020-04432-w

14. Zouboulis CC, Piquero-Martin J. Update and future of systemic acne treatment. *Dermatology*. 2003;206(1):37-53. doi:10.1159/000067821

Published online Aug 3, 2022.