Drug-induced acute interstitial nephritis with cutaneous involvement: characterizing overlapping features with drug-induced hypersensitivity syndrome. A systematic review.

Sigrid Marie Collier, Janewit Wongboonsin, Shanelle Mariah Briggs, Sonya Ahuja, Lihong Bu, Noah Goldfarb

Submitted to: JMIR Dermatology
on: June 17, 2024

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Sigrid Marie Collier[1] MD, MPH; Janewit Wongboonsin[2] MD, MS; Shanelle Mariah Briggs[3] MD; Sonya Ahuja[4] BA; Lihong Bu[5] MD, PhD; Noah Goldfarb[6] MD

[1]Department of Dermatology University of Washington Seattle US
[2]Renal Division Brigham and Women's Hospital Boston US
[3]Department of Dermatology Medical College of Wisconsin Milwaukee US
[4]University of Washington School of Medicine Seattle US
[5]Department of Laboratory Medicine and Pathology Mayo Clinic Rochester US
[6]Department of Dermatology University of Minnesota Minneapolis US

Corresponding Author:
Sigrid Marie Collier MD, MPH
Department of Dermatology
University of Washington
1959 NE Pacific St
Room BB-1332, Box 356524
Seattle
US

Abstract

This systematic review analyzes the clinical overlap and distinction between drug-induced acute interstitial nephritis (DI-AIN) and drug reaction with eosinophilia and systemic symptoms (DRESS), highlighting that 42.8% of published DI-AIN cases with cutaneous involvement meet criteria for DIHS/DRESS, according to the RegiSCAR scoring system.

(JMIR Preprints 17/06/2024:63359)
DOI: https://doi.org/10.2196/preprints.63359

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Sigrid Collier, MD, MPH[1]**, Janewit Wongboonsin, MD, MS [2,3,4] **, Sonya Ahuja, BA[5], Shanelle Briggs, MD[6], Lihong Bu, MD, PhD [7], Noah Goldfarb, MD[2,8,9]

[1]Division of Dermatology, University of Washington Medical Center, Seattle, USA
[2]Department of Medicine, University of Minnesota, Minneapolis, USA
[3]Renal Division, Brigham and Women's Hospital, Massachusetts, USA
[4]Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
[5]School of Medicine, University of Washington, Seattle, USA
[6]Department of Dermatology, Medical College of Wisconsin, Milwaukee, USA
[7]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, USA
[8]Department of Dermatology, University of Minnesota, Minneapolis, USA
[9]Department of Medicine and Dermatology, Minneapolis VA Healthcare System, Minneapolis, USA

**Sigrid Collier and Janewit Wongboonsin equally contributed to this work

Corresponding author:
Sigrid Collier, MD, MPH
Division of Dermatology, University of Washington Medical Center
1959 NE Pacific St, Room BB-1332, Box 356524
Seattle WA 98195-6524
Email: coll0640@uw.edu
Phone: 206-543-5290
Fax: 206-543-2489

Acknowledgements: Portions of this manuscript were presented at the 2022 Society of Investigative Dermatology Conference and subsequently published as an abstract in the Journal of Investigative Dermatology.

Conflicts of Interest: None declared.
IRB approval status: Our study is a systematic review and is IRB exempt PROSPERO (International Prospective Register of Systematic Reviews); no. CRD42020107706

Funding sources: None

Introduction

Acute interstitial nephritis (AIN) is a type IVb delayed hypersensitivity reaction that can cause a rapid decline in kidney function and lead to chronic kidney disease.[1] It can be triggered by a variety of factors, however roughly 70% of cases are caused by drug therapy.[1] In cases where medication is the cause, the condition is referred to as drug-induced acute interstitial nephritis (DI-AIN).[2] Cases of DI-AIN with cutaneous involvement can be difficult to distinguish from cases of drug reaction with eosinophilia and systemic symptoms (DRESS), also referred to as drug-induced hypersensitivity syndrome (DIHS).[3] Moreover, there are reports of DIHS/DRESS with concomitant DI-AIN, since the definitive diagnosis of AIN relies on renal histopathology, whereas DIHS/DRESS is a clinical diagnosis, confirmed using the RegiSCAR scoring system.[4] Nevertheless, it is useful to understand the clinical differences between DI-AIN and DIHS/DRESS, as these conditions have distinct prognoses and treatment protocols. For example, DI-AIN is typically associated with very low mortality rates, while DIHS/DRESS has a mortality rate of around 10%.[4] Furthermore, systemic corticosteroids are the standard of care in DIHS/DRESS, however they are not indicated in all cases of AIN.[2]

Methods

We conducted a systematic literature search in Ovid MEDLINE (1946 to April 9, 2020) to identify studies of adults with biopsy-proven AIN, cutaneous manifestations, and identifiable drug-culprit. EMBASE was excluded due to excessive off-target search results. Observational studies, case series, and case reports were included, while review articles, transplant kidney biopsies, and pediatric cases were excluded, see Figure 1. Additionally, all biopsy findings were reviewed by a renal pathologist to re-confirm the diagnosis of AIN. Two data collectors performed independent review and data abstraction, documenting demographic factors, medication culprit, mortality, dialysis dependence, final creatinine levels, and components of the RegiSCAR criteria, such as fever and eosinophilia. Then, cases were categorized by RegiSCAR score, with definite DIHS/DRESS equating to a score of

6 criteria met and above, probable (score 4 and 5), possible (score 2 and 3), and no DIHS/DRESS (score <2), see Table 1.

Results

We identified 270 studies for screening, of which 37 studies with a total of 43 cases met inclusion criteria. Of the 28 cases with a published diagnosis of only DI-AIN (no concomitant DIHS/DRESS diagnosis), 16 cases (57.1%) met RegiSCAR criteria for no DIHS/DRESS, 10 cases (35.7%) met criteria for possible DIHS/DRESS, and 2 cases (7.1%) met criteria for probable or definite DIHS/DRESS (Table 1). Of the 9 cases published with a diagnosis of both DI-AIN and DIHS/DRESS, all cases met RegiSCAR criteria for possible (22.2%) or probable/definite (77.8%) DIHS/DRESS (Table 1). Specifically, cases with fever, eosinophilia, and liver injury were more likely to meet RegiSCAR criteria for possible or probable DIHS/DRESS. In cases of DI-AIN that did not meet RegiSCAR criteria for DIHS/DRESS, beta-lactams tended to be more common culprit medications. In contrast, vancomycin, anti-epileptics, and allopurinol were more common in cases of DI-AIN that met RegiSCAR criteria for possible or probable DIHS/DRESS. Notably, there were no significant differences in creatinine levels or dialysis dependence between the two groups.

Discussion

This systematic review revealed that 42.8% of cases with a published diagnosis of DI-AIN met RegiSCAR criteria for possible, probable, or definite DIHS/DRESS. Our findings highlight the significant and ongoing challenges in distinguishing DI-AIN from DIHS/DRESS. Furthermore, this study demonstrated that cases of DI-AIN which met RegiSCAR criteria for possible (23.1%) or probable DIHS/DRESS (21.4%) exhibited a higher mortality rate compared to those that did not meet the criteria for DIHS/DRESS (6.25%).

Although illuminating, there are several limitations to this study. First, the cases selected for analysis

consist of a relatively small sample, which might not adequately reflect the full spectrum of DI-AIN with cutaneous involvement. Additionally, the review of biopsy findings was based on the interpretation of images presented in the literature rather than direct examination of tissue samples.

Overall, these results underscore the importance of comprehensive evaluation of features of DIHS/DRESS in cases of DI-AIN, specifically liver injury and eosinophilia. The presence of a severe cutaneous drug reaction should provoke an interdisciplinary discussion on the use of corticosteroids, which may be indicated in cases of DI-AIN that meet criteria for DIHS/DRESS.

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Table 1. “Characterization of Published Cases of AIN with Cutaneous Involvement by RegiSCAR Score.”

	RegiSCAR Categorization		
	DI-AIN (N=16)	**DI-AIN + Possible DIHS *** (N=13)	**DI-AIN + Probable/ Definite DIHS **** (N=14)
Demographics			
Female, N (%)	9 (56.2)	3 (23.1)	6 (42.9)

Male, N (%)	7 (43.8)	10 (76.9)	8 (57.1)
Age; Median (IQR)	51 (45.8, 61)	66 (57, 71)	56.5 (37.5, 68.8)
Publications' Diagnosis			
DI-AIN (N=28)	16 (57.1)	10 (35.7)	2 (7.1)
DI-AIN + DIHS (N=9)	0 (0.0)	2 (22.2)	7 (77.8)
DI-AIN + Other*** (N=6)	0 (0.0)	1 (16.7)	5 (83.3)
RegiSCAR	-0.062	2.615	4.929
Fever, N (%)	4 (25.0)	7 (53.8)	12 (85.7)
Lymphadenopathy, N (%)	0 (0.0)	1 (50.0)	6 (85.7)
Atypical Lymphocytes, N (%)	-	-	100.0%
Eosinophilia, N (%)	5 (45.5)	13 (100.0)	13 (100.0)
Absolute Eosinophil Count, Mean (SD)	726.5 (245.4)	2622.3 (2508.9)	3701.1 (3960.8)
Liver, N (%)	0 (0.0)	4 (30.8)	13 (92.9)
Resolution>15 days, N (%)	7 (63.6)	11 (100.0)	12 (92.3)
> 3 investigations, N (%)	3 (37.5)	1 (100.0)	9 (90.0)
Biopsy with DIHS, N (%)	0 (0.0)	-	2 (50.0)
Missing Data	11 (68.8)	13 (100.0)	10 (71.4)
>50% BSA, N%	0 (0.0)	1 (100.0)	3 (75.0)
Missing Data	11 (68.8)	12 (92.3)	10 (71.4)
Characteristic of DIHS, N (%)	2 (40.0)	1 (100.0)	-
Missing Data	11 (68.8)	12 (92.3)	14 (100)
Drug Culprits* **			
Beta-Lactam, N (%)	4 (25.0)	3 (23.1)	1 (7.7)
Vancomycin, N (%)	1 (6.3)	3 (23.1)	1 (7.7)
Anti-Epileptics, N (%)	0 (0.0)	3 (23.1)	0 (0.0)
Allopurinol, N (%)	0 (0.0)	0 (0.0)	2 (15.4)
Other, N (%)	11 (68.8)	4 (30.8)	9 (69.2)
Creatinine			
< or = 1.5 mg/dl	6 (60.0%)	3 (50.0%)	6 (66.7%)
>1.5 mg/dl	4 (40.0%)	3 (50.0%)	3 (33.3%)
Dialysis Dependent			
No	10 (90.9%)	8 (80.0%)	11 (100.0%)
Yes	1 (9.1%)	2 (20.0%)	0 (0.0%)
Mortality	1 (6.2)	3 (23.1)	3 (21.4)

Table 1 footnote. *RegiSCAR score = 2 OR 3, **RegiSCAR score >= 4, *** Cases describing the

constellation of symptoms associated with DRESS/DIHS published before 1996

Figure 1: Prisma Flow Diagram