

Case Report

Omeprazole Induced Rapid Drug Reaction with Eosinophilia, Systemic Symptoms, and Cross-Reactivity in Delayed-Type Hypersensitivity Associated with Proton-Pump Inhibitors: A Case Report and Literature Review

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Background. Omeprazole, a proton pump inhibitor (PPI), is a widely used and generally safe agent for treating acid-related gastrointestinal conditions. However, drug reaction with eosinophilia and systemic symptoms (DRESSs) syndrome has been reported. **Objectives.** To report a case of omeprazole-induced rapid DRESS syndrome and to review the literature. **Methods.** Descriptive analysis of one new case and a case series from literature review. **Results.** We report a case of 82-year-old woman presenting with rapid-onset of DRESS syndrome. The condition was initially suspected to be caused by antibiotic, but the definite diagnosis was eventually omeprazole-induced DRESS syndrome as suggested by the enzyme-linked immune absorbent spot (ELISpot) assay along with the clinical picture. Previous literatures regarding cases of PPI-induced DRESS syndrome were pooled for descriptive analysis. Among 21 PPI cases pooled, esomeprazole was the most commonly implicated PPI (52.4%), followed by pantoprazole (19.1%), and omeprazole along with lansoprazole (both 14.3%). The issue of cross-reactivities amongst PPIs remains uncertain. Nonetheless, in situations in which a PPIs are deemed necessary, a prudent approach could be considering a switch to an alternative agent with distinct chemical structure. **Conclusion.** PPI is commonly used safely as an agent for acid-related gastrointestinal conditions. However, PPI-induced rapid DRESS syndrome can occur, particularly with prior exposure history. ELISpot is an in vitro test, useful in identifying the culprit agent in patients with delayed-type hypersensitivity reaction.

1. Background

Drug reaction with eosinophilia and systemic symptom (DRESS) is a severe and idiosyncratic drug reaction characterized by T cell-mediated hypersensitivity. The prevalence of DRESS has been estimated at 9.63 cases per 100,000 patients in Thailand and 2.18 per 100,000 in the United States [1, 2]. The development of DRESS involves a complex interaction between drug exposure,

genetic predisposition, and viral reactivation, acting as risk factors and predisposing conditions [3]. Symptoms of DRESS typically emerge between 2 and 8 weeks after exposure to the causative agent [4]. However, individuals with prior exposure may have a shorter time duration between drug initiation and the onset of the reaction. Clinical presentation often includes an erythematous rash often accompanied by itching, facial edema, lymphadenopathy, hematologic abnormalities, visceral involvements,

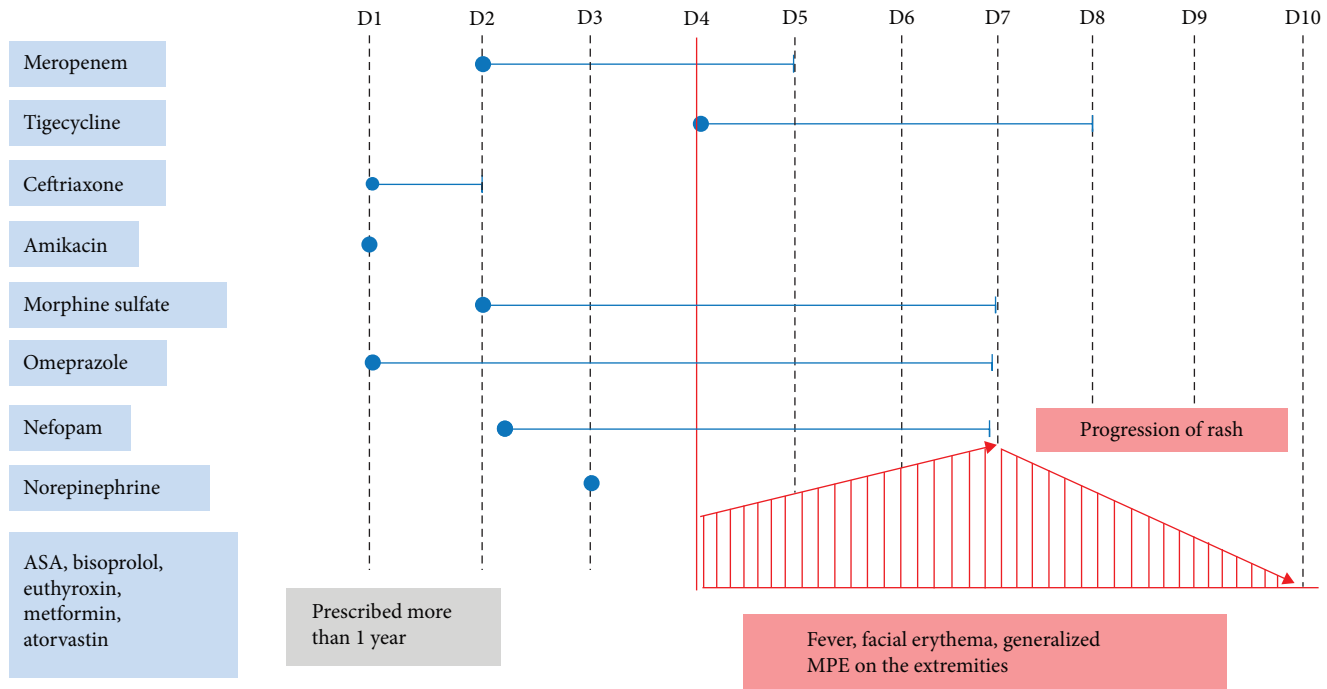


FIGURE 1: Timeline of drug administration and rash progression.

and high-grade fever [5, 6]. Even after discontinuation of the culprit agent, signs and symptoms of DRESS may persist with an average recovery period of 6–9 weeks [7]. Long-term sequelae following DRESS have been reported including autoimmune thyroiditis, fulminant type I diabetes, autoimmune hemolytic anemia, thrombotic thrombocytopenia purpura, and rheumatoid arthritis [3]. The mortality rate associated with DRESS is frequently reported to be approximately 3.8%–10%, which cardiac involvement in DRESS is associated with the highest mortality rate (45.2%–50%), followed by renal involvement (13%), and liver involvement (5%–10%) [8–12].

DRESS is commonly associated with various drugs, including anticonvulsants, allopurinol, sulfonamides, and antibiotics [2, 13]. According to RegiSCAR, aromatic anticonvulsants account for 35% of all cases of DRESS with carbamazepine the most frequent culprit agent. Allopurinol and sulfonamide are attributed to approximately 11%–18% along with 12% of cases, respectively. Although proton pump inhibitors (PPIs) rarely cause DRESS, they have been reported as the causative drug in 0.2%–0.3% of cases [14].

We report one case of omeprazole-induced DRESS syndrome and review the literature of PPI-induced DRESS syndrome cases to elucidate the clinical courses, culprit PPIs, diagnostic evaluations, and clinical outcomes associated with PPI-induced DRESS.

2. Case Presentation

An 82-year-old Thai woman with a history of hypertension, type 2 diabetes mellitus, hypothyroidism, aortic valve replacement, and endometrial cancer presented with fever and abdominal pain for 3 days at the emergency department. The patient was admitted to the hospital and diagnosed with acute cholecystitis,

for which she underwent open cholecystectomy the same day, and received postoperative ceftriaxone (2 g intravenously daily) and omeprazole (40 mg intravenously daily). On Day 2 of hospitalization, ceftriaxone was switched to meropenem due to suspected breakthrough infection. On Day 4 of hospitalization, she had a fever, facial erythema, and edema, as well as a generalized maculopapular rash on the extremities. The timeline of drugs administration and the appearance of skin manifestations is illustrated in Figures 1 and 2, respectively. Blood work revealed mild transaminitis (aspartate transaminase level, 61 U/L) and a slightly increased white blood cell count with eosinophilia (9,870 cells/mm³, eosinophils 8%). Renal function was normal (serum creatinine, 1.1 mg/dL). Based on the RegiSCAR scoring system [15], the patient received a total of two points, indicating a possible diagnosis of DRESS syndrome, including fever ($\geq 38.5^{\circ}\text{C}$) = 0, eosinophilia = 1, extension of skin rash (>50%) = 1, and internal organ involved = 1.

At the time of the initial diagnosis of DRESS, meropenem was suspected to be the culprit agent due to prior reports indicating antibiotics may cause rapid DRESS [16]. Meropenem was consequently promptly discontinued. An allergist was consulted, and they suggested and expressed doubt that meropenem was the culprit agent, citing the short interval between exposure and the onset of symptoms. The progression of the skin rash was additionally documented, which could have been attributable to the persistence of the actual causative agent. Omeprazole was considered as the other likely culprit agent and was discontinued on Day 7 after admission. To confirm the suspected omeprazole-induced DRESS syndrome, an enzyme-linked immunosorbent spot (ELISpot) assay was performed, and the results supported this hypothesis (Table 1). As part of the treatment, the patient was prescribed oral prednisolone at a dose of 15 mg for 5 days.



FIGURE 2: Skin manifestations suspected to be drug reaction with eosinophilia and systemic symptoms syndrome.

TABLE 1: ELISpot results.

Allergen/drugs	Dose	SFU/10 ⁶ PBMC IFN- γ ELISpot
Ceftriaxone	40 μ g/mL	0
Ceftriaxone	200 μ g/mL	0
Ceftriaxone + anti-PD-L1	40 μ g/mL	0
Ceftriaxone + anti-PD-L1	200 μ g/mL	0
Meropenem	40 μ g/mL	0
Meropenem	200 μ g/mL	0
Meropenem + anti-PD-L1	40 μ g/mL	0
Meropenem + anti-PD-L1	200 μ g/mL	0
Omeprazole	1 μ g/mL	0
Omeprazole ^a	5 ng/mL	8
Omeprazole + anti-PD-L1	1 μ g/mL	16
Omeprazole + anti-PD-L1	5 ng/mL	24
PHA	5 mg/mL	3,388

Note: ^aPositive result for ELISpot activation at an omeprazole concentration of 5 ng/mL.

A histamine type-2 receptor antagonist (H2RA) was used for peptic ulcer prophylaxis in place of omeprazole. A gradual resolution of the skin rash, the eosinophilia, and the transaminitis were documented. Prednisolone was tapered at 5 mg every 3 days and then it was continued. On Day 10 of hospitalization prior to discharge, her clinical manifestations of DRESS syndrome had resolved including normalization of the eosinophil count.

2.1. Proton Pump Inhibitors Associated with DRESS: Literature Review. Case reports and related articles reporting on PPI-induced DRESS published between January 2005 and July 2023 were retrieved through keywords searching

of the electronic database MEDLINE[®]/PubMed[®] (last search attempted 6 July 2023), as shown in Table 2.

A total of 21 cases were identified in which PPIs were associated with DRESS syndrome. Amongst these cases, the majority was female with mean \pm SD age of 62.0 \pm 11.3 years. The most commonly identified culprit drug was esomeprazole (11/21, 52.4%), followed by pantoprazole (4/21, 19.1%) and omeprazole along with lansoprazole (both 3/21, 14.3%). Table 3 provides information on the clinical and internal organ involvement observed in these cases. Cross-reactivities between each case's reported culprit PPI and other PPIs are shown in Table 4.

3. Discussion

In the present case report, we have identified a possible case of DRESS with symptoms manifesting merely 4 days after drug exposure. The patient's syndromic presentation was a skin rash, eosinophilia, hepatitis, and acute kidney injury although lymphadenopathy was not observed. Initially, our suspicions fell on meropenem as the causative drugs, prompting us to discontinue its use. However, the progression of the rash and eosinophilia persisted, prompting us to redirect our attention to omeprazole as the potential culprit responsible for the DRESS syndrome in the present case. Subsequently, upon discontinuation of omeprazole, we observed the resolution of skin rash and internal organ involvement.

In retrospective study conducted by Soria et al. [16], a cohort of DRESS syndrome cases with short latency was investigated. Antibiotics and iodinated contrast media emerged as potential causative drugs with a mean \pm SD onset of symptoms at approximately 7.3 \pm 4.0 days after drug exposure. Notably, the short latency group exhibited a significantly lower incidence of lymphadenopathy compared to cases with symptoms appearing greater or equal to 15 days after exposure to the culprit agent. As per our review, the latency period of DRESS from the PPI ranges from 8 to 53 days. However, in some studies, the latency of DRESS could be 2–180 days [27].

Although omeprazole was not identified as a common culprit PPI causing the rapid onset of DRESS syndrome in the aforementioned study [16], it is worth considering the potential role of prior exposure to PPIs, such as omeprazole. PPIs are extensively utilized in both outpatient and in-patient settings for the treatment of gastric ulcers. The consideration gains support from our understanding of DRESS pathogenesis, which involves T cell-mediated hypersensitivity [28]. The presence of preexisting memory T cells could potentially contribute to the accelerated onset of DRESS syndrome observed in the present reported case following exposure to omeprazole.

Currently, clinical diagnosis remains the gold standard for diagnosis of DRESS syndrome. Various factors including the time from drug initiation to the development of delayed reaction, clinical presentation, and the drugs class in relation to specific drug reactions should be evaluated to identify the culprit drug while testing for delayed reactions has limited evidence and is often based on small case series without drug challenge. Patch tests are used for investigating the culprit agents and underlying hypersensitivity mechanisms, but they

TABLE 2: Publication reporting proton pump inhibitors associated with DRESS.

Reference	PPI drug	Age (year)	Sex	Onset (day)	Presentation	Abnormal tests	Remark
Carboni et al. [17]	Esomeprazole	41	F	20	(i) Erythematous and itching skin reaction with maculopapular diffuse lesions, followed by desquamation (ii) Fever	(i) Eosinophilia (ii) Hepatitis	Patch tests were positive with esomeprazole, omeprazole, and pantoprazole
Barbaud et al. [18]	Esomeprazole	64	F	NA	NA	NA	Patch test positive
	Esomeprazole	60	M	NA	NA	NA	Patch test positive
	Pantoprazole	31	F	NA	NA	NA	Patch test positive
	Pantoprazole	51	F	NA	NA	NA	Patch test negative
	Lansoprazole	75	F	NA	NA	NA	Patch test negative
Bourneau-Martin et al. [19]	Omeprazole	88	F	53	(i) Maculopapular exanthema on the trunk and the face converging with wide patches with purpuric lesions (ii) Fever (iii) Lymphadenopathy	(i) Creatinine rising (ii) Eosinophilia (iii) Lymphocytosis	Skin biopsy: inflammatory cell infiltrate rich in neutrophils and lymphocytes
Zatem et al. [20]	Esomeprazole	84	F	8	(i) Fever (ii) Maculopapular rash	(i) Creatinine rising (ii) Eosinophilia (iii) Hepatitis	Dead
Uppalapati and Koneru [21]	Lansoprazole	40	F	30	(i) Pruritis (ii) Generalized maculopapular rash (iii) Palmar erythema	(i) Creatinine rising Eosinophilia (ii) Hyperbilirubinemia	Skin biopsy showed perivascular inflammatory infiltrate with elevated eosinophils
Lin et al. [22]	Pantoprazole (<i>n</i> = 2)	61.9 ± 8.0	NA	27.2 ± 19.1	(i) Skin rash > 50% of the BSA (ii) At least one internal organ abnormality	(i) Atypical lymphocyte (<i>n</i> = 6) (ii) Creatinine rising (<i>n</i> = 3)	—
	Esomeprazole (<i>n</i> = 7)				(iii) One blood work abnormality	(iii) Eosinophilia (<i>n</i> = 8)	
	Lansoprazole				(iv) Lymphadenopathy	(iv) Hepatitis (<i>n</i> = 8)	
					(v) Fever > 38.5°C	(v) Pneumonitis (<i>n</i> = 3)	
He et al. [23]	Omeprazole	66	F	14	(i) Pruritus (ii) Desquamation (iii) Erythema multiforme (iv) Fever	(i) Creatinine rising (ii) Eosinophilia	Renal biopsy: chronic tubular interstitial inflammation diffuse atrophy of the renal tubular epithelium, extensive lymphocytic infiltration of the renal interstitial, and occasionally eosinophils
Present study's case report	Omeprazole	82	F	4	(i) Facial erythema (ii) Facial edema (iii) Generalized maculopapular rash (iv) Fever	(i) Hepatitis (ii) Eosinophilia	ELISpot to omeprazole positive

Note: PPI, proton pump inhibitor; NA, non-applicable; F, female; M, male; BSA, body surface area; ELISpot, enzyme-linked immunosorbent spot.

TABLE 3: Clinical presentation, internal organs involvement, and laboratory abnormalities in proton pump inhibitors induced DRESS in 16 patients.

Characteristics in PPIs-induced DRESS	Percentage affected (<i>n</i> = 16)
Skin rash involve > 50% BSA	100
Fever	93.8
Eosinophilia	87.5
Hepatitis	68.8
Creatinine rising	43.8
Pneumonitis	18.8

Note: BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms syndrome.

TABLE 4: Cross-reactivity among proton-pump inhibitors in delayed type hypersensitivity.

Causative PPI/phenotype	Omeprazole	Pantoprazole	Esomeprazole	Lansoprazole	Dexlansoprazole	Rabeprazole
Omeprazole	—	—	—	—	—	—
Pantoprazole/airborne contact dermatitis	+P [24]	—	+DPT [22]	—	—	—
Pantoprazole/SJS						
Esomeprazole/delayed urticaria esomeprazole/DRESS esomeprazole/MPE	—SPT [25] +P [17]	+SPT [25] +P [17]	—	—DPT [25] —DPT [22]	—DPT [22]	—DPT [22]
esomeprazole/SJS/TEN						
Lansoprazole/pruritic papules lansoprazole/MPE	+P [26]	—DPT [22]	—DPT [22] —DPT [22]	—	—	+DPT [22]
lansoprazole/SJS/TEN						
lansoprazole/DRESS						
Dexlansoprazole/MPE	—	—	—DPT [22]	—	—	+DPT [22]
Rabeprazole	—	—	—	—	—	—

Note: DPT, drug provocation test; P, patch test; PPI, proton pump inhibitor; SPT, skin prick test; —, negative result; +, positive result; MPE, maculopapular eruption; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptom.

have low sensitivity (32%) and require good skin conditions [29]. Instead of patch tests, ELISpot assay and lymphocyte stimulation test can be employed albeit in research laboratories more than routine clinical practice. However, it is important to note that in vitro testing alone cannot definitively confirm or rule out a drug reaction, and clinical history remains the reference standard [30].

As discussed with the patient, the ELISpot assay exhibits the highest sensitivity and specificity in cases of DRESS, with a sensitivity of 61% and specificity of 97% [16]. However, the sensitivity and specificity of the ELISpot depend on factors such as Naranjo score, drug allergy phenotype, type of suspected drug, and underlying disease, as mentioned in Chongpison et al.'s [31] study. The confidence score calculated by machine learning for omeprazole was 0.80 (percentage of positive challenge 68.8), while for meropenem and ceftriaxone, it was 0.15 (percentage of positive challenge around 13.1) (as Figure 3). This suggests that she might be experiencing DRESS due to omeprazole rather than an antibiotic. In this case, our plan of action is to conduct skin tests and provocation tests using ceftriaxone and meropenem in an outpatient setting. However, on the next visit, she was receiving ceftriaxone without same reaction.

Previous studies have reported promising results for the ELISpot assay in identifying the culprit agent with a sensitivity of 70% in DRESS syndrome patients [33–35]. Supplementation

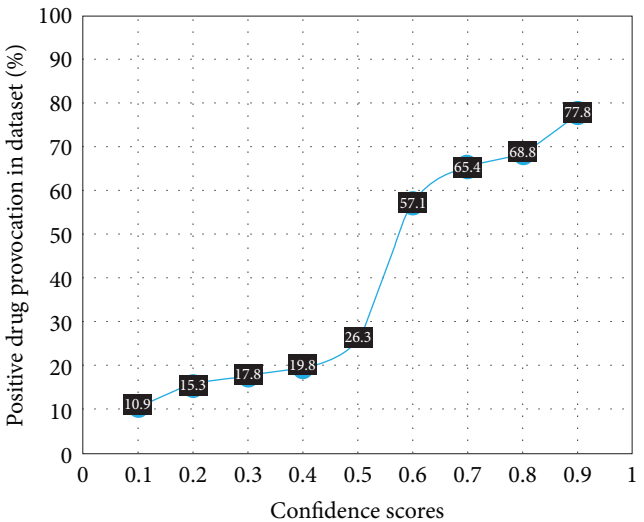


FIGURE 3: Predictive model conceived from 1,024 ELISpot assays and 165 drug challenges. Source: Hipaa's [32] study.

with anti-PD-1 significantly increased the frequencies of drug-induced IFN- γ -releasing cells. A positive ELISpot assay result was determined by frequencies of drug-induced IFN- γ reaching 17.2 SFU/10⁶ PBMCs [36]. In our case, the ELISpot assay using f omeprazole and anti-PD-1at 5 ng/mL produced positive results

with frequencies of drug-induced IFN- γ of 24 SFU/10⁶ PBMCs. A previous study nonetheless reported a specificity of 82.9% for the ELISpot assay in the detection of beta-lactam hypersensitivity [37].

To prevent repeated drug reactions, particularly in severe cutaneous adverse reactions, it is imperative to carefully evaluate the potential for cross-reactivity between the implicated drugs and other agents. However, the issue of cross-reactivity among PPIs remains a matter of ongoing debate due to the lack of a definite understanding of the underlying mechanism. In a study conducted in Taiwan involving 69 cases of PPI-related delayed-type hypersensitivity, 10 cases of DRESS syndrome were identified. Among these cases, esomeprazole emerged as the PPI most frequently associated with delayed-type hypersensitivity reaction. Interestingly, alternative PPIs with distinct chemical structures were administered to 15 patients, resulting in improved tolerance. These findings suggest that individuals with a history of PPI-induced delayed-type hypersensitivity may benefit from avoiding PPIs that share similar chemical structures [22]. It is noteworthy, however, that even drugs with disparate chemical structures, such as lansoprazole and omeprazole, can still demonstrate cross-reactivity in certain instances. Clinicians should, therefore, be cautious when managing such patients [22].

The present study has a limitation. It lacked viral studies including assessments of HHV6, HHV7, CMV, and EBV viral loads. The present study nonetheless encompassed clinical evaluations and in vitro investigations, such as ELISpot assay.

In conclusion, clinicians must not overlook the possibility of PPI-induced DRESS syndrome. Identifying the culprit agent is essential for effective long-term management, particularly in individuals requiring acid suppression. Non-PPI treatment options can be considered due to limited data on cross-reactivity. In cases in which a PPI is deemed necessary, switching to an alternative with distinct chemical structure, coupled with long-term follow-up, and appropriate drug labeling to prevent future exposure may, however, be advisable.

Data Availability

The data used to support the finding of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

- [1] A. Hiransuthikul, T. Rattananupong, J. Klaewsongkram, P. Rerknimitr, M. Pongprutthipan, and K. Ruxrungtham, "Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS): 11 years retrospective study in Thailand," *Allergology International*, vol. 65, no. 4, pp. 432–438, 2016.
- [2] A. R. Wolfson, L. Zhou, Y. Li, N. A. Phadke, O. A. Chow, and K. G. Blumenthal, "Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome identified in the electronic health record allergy module," *The Journal of Allergy and Clinical Immunology: In Practice*, vol. 7, no. 2, pp. 633–640, 2019.
- [3] H. Stirton, N. H. Shear, and R. P. Dodiuk-Gad, "Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS)—readdressing the DRESS," *Biomedicine*, vol. 10, no. 5, Article ID 999, 2022.
- [4] Y. Mizukawa, K. Hirahara, Y. Kano, and T. Shiohara, "Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms severity score: a useful tool for assessing disease severity and predicting fatal cytomegalovirus disease," *Journal of the American Academy of Dermatology*, vol. 80, no. 3, pp. 670–678.e2, 2019.
- [5] V. Descamps, "DRESS syndrome," *The Lancet*, vol. 400, no. 10352, Article ID 560, 2022.
- [6] J. C. Roujeau and R. S. Stern, "Severe adverse cutaneous reactions to drugs," *The New England Journal of Medicine*, vol. 331, pp. 1272–1285, 1994.
- [7] P. Cacoub, P. Musette, V. Descamps et al., "The DRESS syndrome: a literature review," *The American Journal of Medicine*, vol. 124, no. 7, pp. 588–597, 2011.
- [8] Y.-C. Chen, H.-C. Chiu, and C.-Y. Chu, "Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases," *Archives of Dermatology*, vol. 146, no. 12, pp. 1373–1379, 2010.
- [9] M. D. da Silva, S. M. Domingues, S. Oluic et al., "Renal manifestations of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review of 71 cases," *Journal of Clinical Medicine*, vol. 12, no. 14, Article ID 4576, 2023.
- [10] S. A. Martinez-Cabriales, N. H. Shear, and E. I. Gonzalez-Moreno, "Liver involvement in the drug reaction, eosinophilia, and systemic symptoms syndrome," *World Journal of Clinical Cases*, vol. 7, no. 6, pp. 705–716, 2019.
- [11] M. Radovanovic, D. Jevtic, A. D. Calvin et al., "Heart in DRESS": cardiac manifestations, treatment and outcome of patients with drug reaction with eosinophilia and systemic symptoms syndrome: a systematic review," *Journal of Clinical Medicine*, vol. 11, no. 3, Article ID 704, 2022.
- [12] J. Intarasupht, A. Kanchanomai, W. Leelasattakul, T. Chantrarat, A. Nakakes, and W. Tiyanon, "Prevalence, risk factors, and mortality outcome in the drug reaction with eosinophilia and systemic symptoms patients with cardiac involvement," *International Journal of Dermatology*, vol. 57, no. 10, pp. 1187–1191, 2018.
- [13] S. H. Kardaun, P. Sekula, L. Valeyrie-Allanore et al., "Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study," *The British Journal of Dermatology*, vol. 169, no. 5, pp. 1071–1080, 2013.
- [14] I. J. Simpson, M. R. Marshall, H. Pilmor et al., "Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases," *Nephrology*, vol. 11, no. 5, pp. 381–385, 2006.
- [15] Y.-T. Cho, C.-W. Yang, and C.-Y. Chu, "Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system," *International Journal of Molecular Sciences*, vol. 18, no. 6, Article ID 1243, 2017.
- [16] A. Soria, C. Bernier, G. Veyrac, A. Barbaud, E. Puymirat, and B. Milpied, "Drug reaction with eosinophilia and systemic symptoms may occur within 2 weeks of drug exposure: a

- retrospective study,” *Journal of the American Academy of Dermatology*, vol. 82, no. 3, pp. 606–611, 2020.
- [17] S. Caboni, N. Gunera-Saad, S. Ktiouet-Abassi, F. Berard, and J. F. Nicolas, “Esomeprazole-induced DRESS syndrome. Studies of cross-reactivity among proton-pump inhibitor drugs,” *European Journal of Allergy and Immunology*, vol. 62, no. 11, pp. 1342–1343, 2007.
 - [18] A. Barbaud, E. Collet, B. Milpied et al., “A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions,” *The British Journal of Dermatology*, vol. 168, no. 3, pp. 555–562, 2013.
 - [19] D. Bourneau-Martin, C. Leclech, A. Jamet et al., “Omeprazole-induced drug reaction with eosinophilia and systemic symptoms (DRESS),” *European Journal of Dermatology*, vol. 24, no. 3, pp. 413–415, 2014.
 - [20] A. Zaïem, O. Charfi, T. Badri, and S. Elaidli, “Fatal outcome of DRESS syndrome associated with esomeprazole,” *Indian Journal of Dermatology, Venereology and Leprology*, vol. 81, no. 4, pp. 407–408, 2015.
 - [21] A. Uppalapati, S. Gogineni, S. Koneru, and G. Kamel, “Are proton pump inhibitors (PPI) naive? A case of drug reaction with eosinophilia and systemic symptom (DRESS) secondary to lansoprazole,” *Aspergillus and Aspergillosis*, vol. 133, Article ID 943, 2015.
 - [22] C.-Y. Lin, C.-W. Wang, C.-Y. R. Hui et al., “Delayed-type hypersensitivity reactions induced by proton pump inhibitors: a clinical and *in vitro* T-cell reactivity study,” *Allergy*, vol. 73, no. 1, pp. 221–229, 2018.
 - [23] Q. He, G. Ying, X. Fei et al., “Drug rash with eosinophilia and systemic symptoms and severe renal injury induced by proton pump inhibitor therapy: a case report,” *Medicine*, vol. 99, no. 42, Article ID e22509, 2020.
 - [24] M. Neumark, A. Ingber, M. Levin, and D. Slodownik, “Occupational airborne contact dermatitis caused by pantoprazole,” *Contact Dermatitis*, vol. 64, no. 1, pp. 60–61, 2011.
 - [25] G. Zisa, L. Bommarito, F. Riccobono, J. Scibilia, and M. Galimberti, “Non immediate-type hypersensitivity reactions to proton pump inhibitors,” *Austin Journal of Allergy*, vol. 1, no. 2, 2014.
 - [26] J. Vilaplana and C. Romaguera, “Allergic contact dermatitis due to lansoprazole, a proton pump inhibitor,” *Contact Dermatitis*, vol. 44, no. 1, pp. 39–40, 2001.
 - [27] P. Wongkitisophon, K. Chanprapaph, P. Rattanakaemakorn, and V. Vachiramon, “Six-year retrospective review of drug reaction with eosinophilia and systemic symptoms,” *Acta dermato-Venereologica*, vol. 92, no. 2, pp. 200–205, 2012.
 - [28] E. M. Schunkert and S. J. Divito, “Updates and insights in the diagnosis and management of DRESS syndrome,” *Current Dermatology Reports*, vol. 10, pp. 192–204, 2021.
 - [29] F. Santiago, M. Gonalo, R. Vieira, S. Coelho, and A. Figueiredo, “Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS),” *Contact Dermatitis*, vol. 62, no. 1, pp. 47–53, 2010.
 - [30] D. A. Khan, A. Banerji, K. G. Blumenthal et al., “Drug allergy: a 2022 practice parameter update,” *The Journal of Allergy and Clinical Immunology*, vol. 150, no. 6, pp. 1333–1393, 2022.
 - [31] Y. Chongpison, S. Sriswasdi, S. Buranapraditkun et al., “IFN- γ ELISpot-enabled machine learning for culprit drug identification in nonimmediate drug hypersensitivity,” *The Journal of Allergy and Clinical Immunology*, 2023.
 - [32] Hipaa, “The confidence score for culprit drug identification in non-immediate cutaneous reactions,” <https://hipaa.jotform.com/213002295249450>.
 - [33] B. Tanvarasethee, S. Buranapraditkun, and J. Klaewsongkram, “The potential of using enzyme-linked immunospot to diagnose cephalosporin-induced maculopapular exanthems,” *Acta Dermato-Venereologica*, vol. 93, no. 1, pp. 66–69, 2013.
 - [34] N. Suthumchai, Y. Srinoulprasert, P. Thantiworasit et al., “The measurement of drug-induced interferon γ -releasing cells and lymphocyte proliferation in severe cutaneous adverse reactions,” *Journal of the European Academy of Dermatology and Venereology (JEADV)*, vol. 32, no. 6, pp. 992–998, 2018.
 - [35] J. Klaewsongkram, C. Sukasem, P. Thantiworasit et al., “Analysis of HLA-B allelic variation and IFN- γ ELISpot responses in patients with severe cutaneous adverse reactions associated with drugs,” *The Journal of Allergy and Clinical Immunology: In Practice*, vol. 7, no. 1, pp. 219–227.e4, 2019.
 - [36] J. Klaewsongkram, S. Buranapraditkun, P. Thantiworasit et al., “The role of *in vitro* detection of drug-specific mediator-releasing cells to diagnose different phenotypes of severe cutaneous adverse reactions,” *Allergy, Asthma & Immunology Research*, vol. 13, no. 6, pp. 896–907, 2021.
 - [37] S. Drygala, E. Rdzanek, G. Porebski, and P. Dubiela, “*In vitro* assays for diagnosis of drug-induced nonsevere exanthemas: a systematic review and meta-analysis,” *Journal of Immunological Research*, vol. 2022, Article ID 2386654, 17 pages, 2022.