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CASE REPORT

Drug Reaction with Eosinophilia and Systemic Symptoms Induced by Diosmin and Hesperidin: A Case Report

Pasita Palakornkitti, Teerapong Rattananukrom

Division of Dermatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Correspondence: Teerapong Rattananukrom, Division of Dermatology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok, 10400, Thailand, Tel +662-201-1141, Fax +662-201-1211, Email teerpongrattananukrom@gmail.com

Abstract: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse reaction which exhibits a diverse range of presentations. We described a 48-year-old man diagnosed with acute generalized exanthematous pustulosis (AGEP)-like DRESS following the administration of diosmin and hesperidin. To our knowledge, diosmin and hesperidin-induced DRESS are exceptionally rare. This aims to raise awareness of potential severe cutaneous side effects in patients taking these agents.

Keywords: chronic venous insufficiency, daflon, facial edema, flavonoid, severe cutaneous adverse reactions

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome represents severe cutaneous adverse reactions (SCARs) posing a non-negligible fatal risk. Clinical manifestations typically occur within 2 to 6 weeks subsequent to the introduction of the causative drug. A hallmark characteristic involves an initial onset marked by high-grade fever followed by diffuse maculopapular eruptions. Additionally, common findings include facial edema, lymphadenopathy, eosinophilia, and internal organ involvement.[1,2] Fulminant liver failure is found to be the most common cause of death.[3] As immediate withdrawal of the offending drug and systemic corticosteroids to control systemic involvement constitutes a mainstream therapy for DRESS, identifying the offending drug is necessary.

Diosmin and hesperidin are flavanone compounds belonging to the subclass of flavonoids, commonly found in citrus fruits. Their benefits include antioxidant, anti-inflammation, antimicrobial, anticarcinogenic properties, among others[4–6] Due to these beneficial effects, diosmin and hesperidin are utilized in the treatment of various conditions, including chronic venous insufficiency, hemorrhoids, and idiopathic epistaxis.[7–11] Previous studies revealed that diosmin and hesperidin are well-tolerated without any serious side effects.[4,10,11] Here, we report a case of acute generalized exanthematous pustulosis (AGEP)-like DRESS subsequent to the administration of diosmin and hesperidin.

Case Report

A 48-year-old man with underlying diseases including hypertension, dyslipidemia, type 2 diabetes, obstructive sleep apnea, and chronic venous insufficiency presented with facial edema and skin eruption on his trunk and extremities persisting for 5 days. Fever had developed 2 days prior to his arrival. Upon his visit to dermatological department, he exhibited a fever (38.8°C) and pronounced facial and hand edema. The dermatological examination showed multiple ill-defined edematous erythematous papules and plaques, accompanied by scattered tiny non-follicular pustules in the earlier stage and followed by small collarettes of desquamation on his face, neck, upper chest, back and extremities, extending to more than 50% of the body surface area (Figure 1). Facial edema was seen; however, no mucosal involvement, lymphadenopathy, and hepatosplenomegaly was reported.

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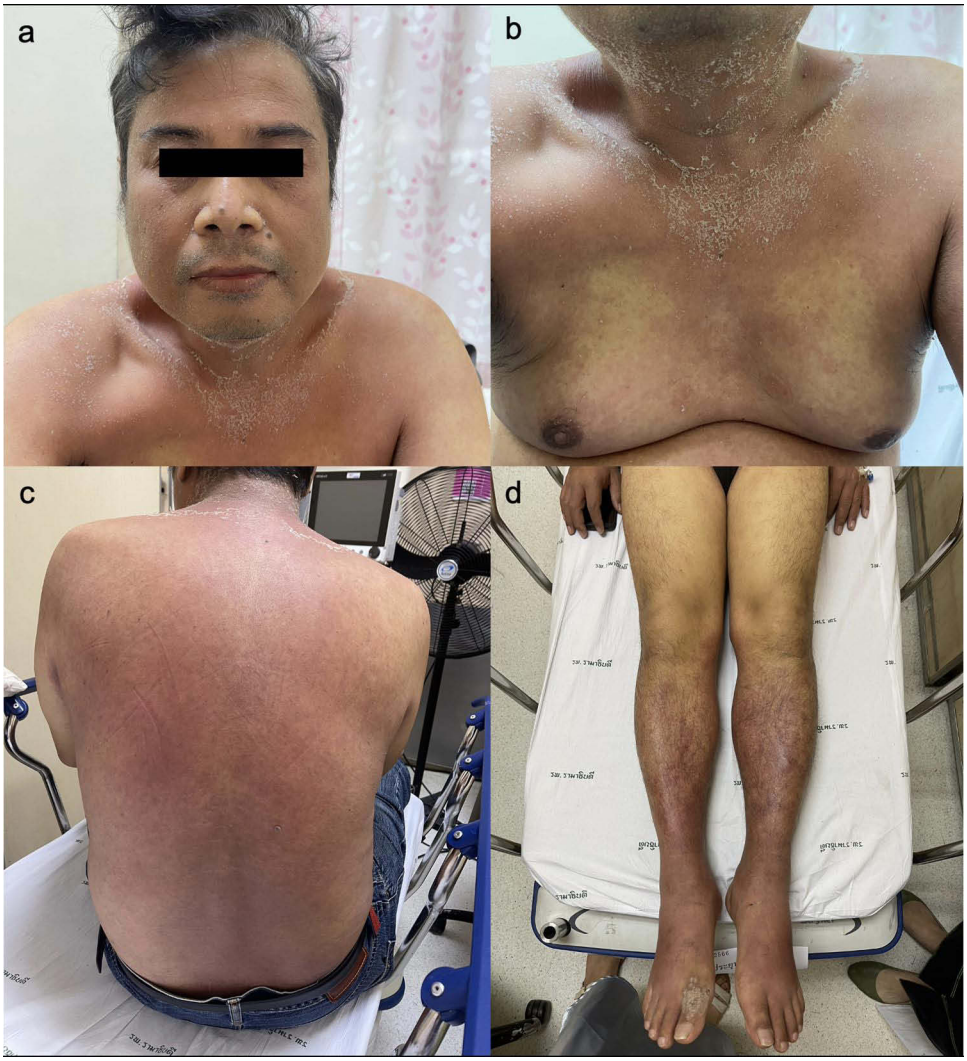

Figure 1 A 48-year-old man experiencing multiple ill-defined edematous erythematous papules and plaques, accompanied by small collarettes of desquamation on his face and neck (**a**), upper chest and back (**b** and **c**), and extremities (**d**).

His current medications were reviewed, including enalapril, rosuvastatin, linagliptin, and metformin, which he had been taking for several years. Recently diagnosed with chronic venous insufficiency, he commenced oral intake of micronized purified flavonoid fraction 1000 mg (Daflon®, Laboratories Servier, France), containing diosmin 900 mg and hesperidin 100 mg, twice daily, starting 24 days ago.

Laboratory tests revealed leukocytosis (white blood cell count, $12\times10^3/\mu L$) with eosinophilia (1200 or 10%) and atypical lymphocytosis (1%). Mild elevations were noted in the aspartate aminotransferase level (AST: 47 U/L [normal range 5–34]) and alanine aminotransferase level (ALT: 89 U/L [normal range 0–55]). Creatinine (1.19 mg/dL [normal range 0.55–1.02]) were detected. Urine proteinuria, and red blood cells were not found. Hepatitis B and C were not detected.

Due to the nature of the skin eruption, the differential diagnosis in this patient included AGEP-like DRESS or AGEP. Unfortunately, our patient declined to undergo a skin biopsy, thus hindering our ability to obtain histopathology support. We suspected a diagnosis of DRESS in this patient based on several factors, including the time interval from initiation of therapy, which was 24 days; facial involvement; and the presence of a mixture of erythematous, edematous eruption, and pustules, which could indicate the morphology of DRESS. Additionally, systemic involvement and laboratory findings of hypereosinophilia and atypical lymphocytes as well as a resolution time longer than 15 days, further supported this suspicion. In contrast, AGEP is characterized by tiny non-follicular pustules and desquamation and typically occurs within 48 hours following exposure to the causative drug. Systemic involvement, including renal, and hepatic

manifestations, is rare in AGEP, and skin resolution usually occurs in less than 15 days. These reasons did not support a diagnosis of AGEP in this case.

Applying the European Registry of Severe Cutaneous Adverse Reactions (RegiSCARs) scoring system, the patient was classified as a probable case of DRESS, achieving a score of 4. This score was determined based on the following criteria: fever (0), eosinophilia (1), presence of atypical lymphocytes (1), extent of skin involvement (1), rash suggesting DRESS (1), absence of skin biopsy (−1), mild transaminitis (1), and resolution of rash taking more than 15 days (0).

The Naranjo scale,[12] a standardized causality assessment of adverse drug reactions (ADRs), showed a score of 6, derived from the following item: no previous conclusive report (0), ADR appearance after drug administration (2), ADR improvement after drug discontinuation (1), unknown drug readministration (0), no alterative cause (2), unknown reaction following placebo (0), unknown plasma drug concentration (0), unknown dose–reaction relationship (0), no previous exposure of the drug (0), and confirmation by objective evidence (1). Therefore, the probability of suspected ADR was probable.[13]

Despite its rarity, micronized purified flavonoid fraction was the most suspected offending drug responsible for DRESS because the latency period between initiation of the drug and development of rash (24 days) was compatible with the course of DRESS. To aid the diagnosis, the IFN-γ enzyme-linked immunospot (ELISPOT) assay was sent for micronized purified flavonoid fraction. The test measured the level of drug-specific IFN- γ releasing cells. The results showed that Daflon®+Anti-PD-L1 at dose of 10 and 100 µg/mL showed IFN-γ ELISPOT levels of 56 and 28 spot-forming units (SFU) per 10^6 peripheral blood mononuclear cells (PBMCs), respectively. Phytohemagglutinin-L (PHA) is a positive control, showing that PHA at 5 µg/mL has an IFN-γ ELISPOT level of 2500 SFU per 10^6 PBMCs. The IFN-γ ELISPOT assay exhibited a positive result for micronized purified flavonoid fraction (Daflon®). The confidence score for culprit drug identification in non-immediate cutaneous reactions was 0.96, correlating with 80% of patient experiencing symptoms upon re-exposure to the drug.

Upon considering the clinical course, drug timeline, and systemic involvement, a diagnosis of AGEP-like DRESS due to diosmin and hesperidin was established. The offending drug was discontinued, and the patient was treated with systemic corticosteroids (prednisolone 30 mg/day) and antihistamine. Fever subsided after 4 days of treatment, and the cutaneous eruption resolved, accompanied by widespread desquamation. Abnormalities of hematologic, liver, and renal function subsequently improved over 4 weeks along with a gradual tapering of oral corticosteroids. Clear skin was achieved after 8 weeks (Figure 2), and oral corticosteroid was discontinued after 12 weeks of treatment.

Discussion

Cutaneous eruptions associated with DRESS exhibit a diverse range of presentations; however, the morbilliform eruption is the most common presentation. This characteristic rash is typically diffuse, macular and exanthema, progressing to edematous state with follicular accentuation. It usually begins on the face, upper trunk, and upper extremities, and eventually spreads to the lower extremities. Pruritus usually presents in associated with the cutaneous eruption. Additional cutaneous manifestations include vesicles, bullae, atypical targetoid plaques, purpura, and occasionally sterile small pustules. The common causative agents are aromatic anticonvulsants and sulfonamides.[1,2,14] Besides clinical and laboratory investigation, drug timeline and individual setting (eg, underlying diseases) are needed to consider before making an accurate diagnosis. Diagnostic criteria (eg, RegiSCARs) is considered to be a useful tool for aiding the diagnosis, particularly in case with atypical features or uncommon causative agent.[1]

Flavonoids are phytochemicals consisting of a group of polyphenolic compounds sharing a benzo-γ-pyrone structure with different degrees of hydroxylation. The configuration, number of hydroxyl groups, and substitution of functional groups define their pharmacokinetics and biological activity.[15] Hence, flavonoids offer versatile pharmacological benefits depending upon its chemical structure.

Chemically, hesperidin is a flavanone glycoside (3,5,7-trihydroxyflavanone 7-rhamnoglucoside, hesperetin-7-*O*-rutino-side) and diosmin is obtained by the dehydrogenation of hesperidin (3',5,7-trihydroxy-4'-methoxyflavone 7-rhamnoglucoside, 3',5,7-trihydroxy-4'-methoxyflavone-7-rutinoside, diosmetin 7-neohesperidoside, and diosmetin 7-O-rutinoside).[6] The combination of diosmin and hesperidin has been use as an oral phlebotonic and venoprotective agent mainly for treating venous disorders.[5–7] Several toxicological studies of this combination were conducted in

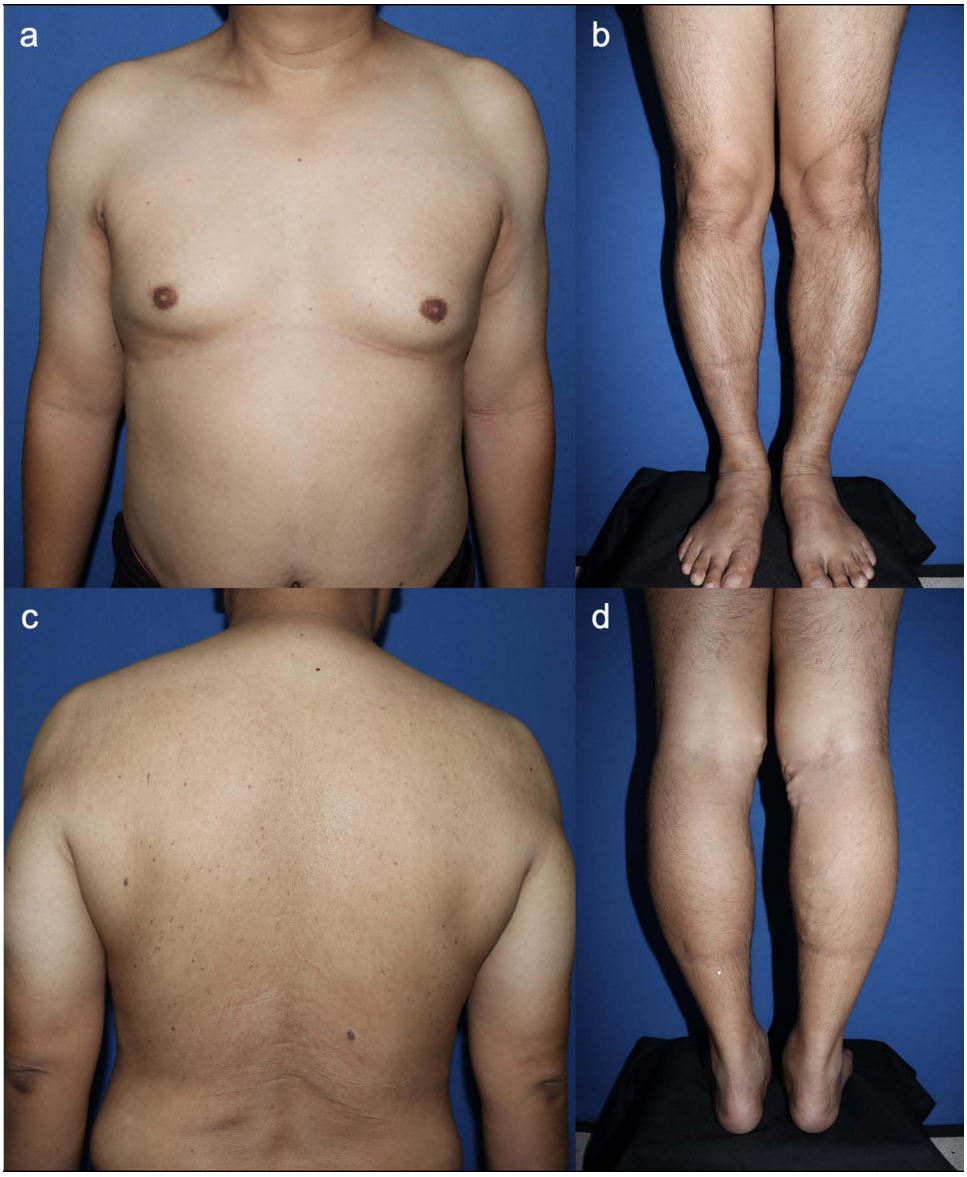

Figure 2 Skin resolution occurred after receiving prednisolone 30 mg/day with a gradual taper off over 8 weeks of treatment and prednisolone was discontinued after 12 weeks of treatment. The skin resolution of the trunk (**a** and **c**) and extremities (**b** and **d**) was demonstrated.

animals and revealed a non-toxic profile.[16,17] Previous clinical studies in human also demonstrated a favorable safety profile. Only one ADR was reported in a 65-years-old female who developed occasional shortness of breath and chest tightness 18 days after using diosmin and hesperidin. Her symptoms were relieved by bronchodilators and disappeared within a few days following drug discontinuation.[18] Other reported ADRs were mild including dyspepsia, nausea, diarrhea, weight loss, headache, and vertigo.[6,10,11,19–22] No severe cutaneous adverse reaction was observed for other subclasses of flavonoids. Additionally, cross reactions between micronized purified flavonoid fraction and other substances have not been previously reported.

To the best of our knowledge, this is the first reported case of AGEP-like DRESS caused by diosmin and hesperidin. We encountered diagnostic challenges in this case because of the overlapping clinical features between AGEP-like DRESS and AGEP, and uncommonness of the causative drug. With the presentation of tiny non-follicular pustules and desquamation, AGEP was included in differential diagnosis in our case. However, AGEP usually occurs within 48 hours following causative drug exposure. Hence, the possibility of AGEP was lessen.[23] Due to the extent of the skin lesion, systemic involvement, the slow resolution of the skin rash (taking more than 15 days), coupled with a RegiSCARs score

of 4, AGEP-like DRESS was suspected. However, our patient declined to undergo a skin biopsy, limiting the histological findings of DRESS.

Recently, the role of in vitro tests in identifying the causative underlying drug for SCAR is highlighted due to the severe nature of these reactions. ELISPOT is an in vitro test developed to measure specific cytokines and cytotoxic markers produced by drug-specific T-cells.[24,25] The optimal timing to perform ELISPOT is within 30 days. The sensitivity and specificity of ELISPOT for identification of culprit drug in DRESS are 61% and 97%, respectively.[25] The use of ELISPOT can make a major contribution in casual diagnosis of drug hypersensitivity, particularly in case with uncommon causative drug. Our case exhibited a positive result in the ELISPOT assay for micronized purified flavonoid fraction, confirming the presence of a possible causative agent.

Conclusion

DRESS syndrome manifests with a variety of cutaneous eruptions. We have highlighted the case of AGEP-like DRESS associated with diosmin and hesperidin. While possible non-cutaneous ADRs of these drugs such as dyspepsia, nausea, diarrhea, weight loss, headache, shortness of breath and vertigo have been reported, the potentially life-threatening ADR of DRESS due to diosmin and hesperidin is rare but exists. This emphasizes the importance of recognizing this rare side effect. Patients should be informed about the potential for cutaneous reactions, and immediate treatment is advised.

Abbreviation

ADR, adverse drug reaction; AGEP, acute generalized exanthematous pustulosis; DRESS, Drug reaction with eosinophilia and systemic symptoms; ELISPOT, enzyme-linked immunospot; RegiSCARs, European Registry of Severe Cutaneous Adverse Reactions; SCARs, severe cutaneous adverse reactions.

Ethics Approval and Informed Consent

The authors certify that they have obtained all appropriate patient consent forms. The patient gave written informed consent for the publication of clinical information and photographs. Institutional approval was not required for this case details.

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Disclosure

The authors declare that this manuscript was prepared in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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