

Drug rash with eosinophilia and systemic symptoms caused by the dietary supplement diindolylmethane



Thuy-My Le, MD, PhD^a, Cornelus J.G. Sanders, MD^a,
Lisette van de Corput, PhD^b,
Karel J. van Erpecum, MD, PhD^c, and
Heike Röckmann, MD, PhD^a

Clinical Implications

- Diindolylmethane, a dietary supplement and potential investigational drug, can cause drug rash with eosinophilia and systemic symptoms, a severe drug reaction. The drug patch test was safe and useful in the diagnosis. This case stresses the importance of obtaining a complete drug history, including use of dietary supplements.

TO THE EDITOR:

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe adverse drug reaction that is potentially life threatening with a mortality rate up to 10%.^{1,2} It is characterized by a variable combination of severe skin eruption, fever, lymphocyte activation (enlarged lymph nodes and atypical lymphocytes), eosinophilia, and internal organ involvement of which the liver is the most common affected organ.³ Compared with other cutaneous drug reactions, DRESS is characterized by a late onset, usually 2-8 weeks after the initiation of the drug (mainly antiepileptic drugs, allopurinol, and antibiotics) therapy, and a longer duration of symptoms despite discontinuation of the culprit drug.^{1,4}

For the first time, we report a case of DRESS that is caused by a dietary supplement. Our patient reacted to diindolylmethane (DIM), which is derived from cruciferous vegetables such as broccoli, cauliflower, cabbage, kale, and Brussels sprouts. It is also an investigational drug being used in treating conditions related to human papilloma virus infection, such as cervical intraepithelial neoplasia and recurrent respiratory papillomatosis, and it is considered a potential chemopreventive agent.⁵ The current frequency of DIM consumption is unknown. Previous studies on the safety of DIM showed no severe adverse reactions.⁶

CASE

A 36-year-old woman presented with an itching and painful rash since 1 week and facial edema for 2 days. She had used 1 tablet of naproxen 220 mg for 2 days before she developed the symptoms. Four weeks before the skin rash, she started to take the dietary supplement DIM complex that consisted of diindolylmethane, broccoli powder, and vitamin E. At least more than 10 weeks before the development of the symptoms, ingestion of vitamin B complex was started (vitamin B1, B2, B3, B5, B6, B12, folic acid, chromium, and creatine).

Physical examination at hospital admission showed generalized painful erythema that covered approximately 70% of the

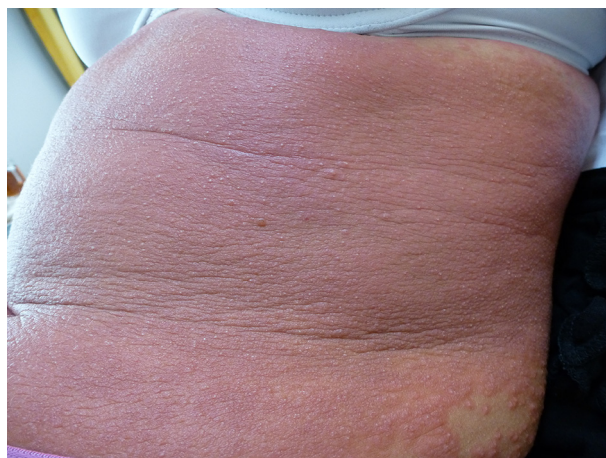


FIGURE 1. Skin rash with erythema and pustules.



FIGURE 2. Drug patch tests with naproxen, DIM complex, vitamin B12 complex, vitamin B1, vitamin B2, vitamin B6, vitamin B12, and folic acid. Only patch testing with all DIM complex concentrations was positive (numbers 2, 3, 4, and 5).

body surface area (Figure 1). Multiple pustules were observed in the erythema. The patient had edema of the face, hands, and feet. Her temperature was 38.6°C.

Laboratory results at admission showed eosinophilia of $6.14 \times 10^9/L$ (reference range $0-0.40 \times 10^9/L$), atypical lymphocytes 0.37 (normal level 0), and abnormal liver biochemistry tests (alanine aminotransferase 116 IU/L [range 0-35 IU/L], aspartate aminotransferase 41 IU/L [range 0-30 IU/L], gamma glutamyl transaminase 251 IU/L [range 0-40 IU/L], alkaline phosphatase 235 IU/L [range 0-120 IU/L], lactate dehydrogenase 288 IU/L [range 0-250 IU/L]). Skin biopsy showed follicular subcorneal pustules and a dermal lymphocytic infiltrate with eosinophils.

The DIM complex and vitamin B complex were discontinued; naproxen had been stopped before. Prednisone 70 mg/day was started and was tapered off within 8 days because of secondary impetiginization of facial skin that was clinically expressed by honey-colored crusts. She was treated with topical fusidic acid in

her face and with topical betamethasone dipropionate 0.1% for the rest of her integument. As new drugs may exacerbate the clinical condition because of nonspecific immune response and stimulatory effects, we avoided systemic antibiotics. The impetigo improved within 1 week. Three weeks after the onset of symptoms, the cutaneous symptoms and clinical condition had improved substantially, and the patient was discharged with betamethasone dipropionate 0.1% treatment once daily. However, laboratory results showed progressive deterioration of the liver biochemistry with most pronounced abnormalities at 4 weeks: alanine aminotransferase 1146 IU/L, aspartate aminotransferase 540 IU/L, gamma glutamyl transaminase 157 IU/L, alkaline phosphatase 161 IU/L, and lactate dehydrogenase 392 IU/L. Bilirubin, prothrombin time, thrombocytes, and albumin were in the normal range. Microbial assays (hepatitis A, B, and C) did not yield an underlying cause for the liver failure. Anti-mitochondrial antibodies and anti-M2 were strongly positive. Antinuclear antibodies were negative. The patient was in good clinical condition, treated with betamethasone dipropionate 0.1% 4 times a week for her skin, and monitored with frequent laboratory testing. After 6 weeks, liver biochemistry normalized, whereas antimitochondrial antibodies persisted. A diagnosis of primary biliary cirrhosis is excluded because of normal bilirubin, liver biochemistry, and absence of clinical symptoms. Nevertheless, considering the persistence of strongly positive anti-mitochondrial antibodies after recovery, there remains a considerable risk of development of overt primary biliary cirrhosis in the future.

Ten weeks after the resolution of symptoms, drug patch tests were performed with the following dilutions: naproxen 10% and 30% in petrolatum, DIM complex 10% and 30% in petrolatum and in water, and vitamin B12 complex 10% and 30% in petrolatum and in water. Vitamin B1, vitamin B2, vitamin B6, vitamin B12, and folic acid were tested separately at a concentration of 1% and 5% in petrolatum. Patch testing with all DIM complex concentration was positive (2+) (Figure 2). The manufacturer of the DIM complex provided the individual ingredients for further testing by the drug patch test. One capsule of DIM complex was composed of 125 mg DIM, 25 mg broccoli extract, 2.35 mg vitamin E extract, and rice meal extract. The latter 3 tested negative in the drug patch test. Dilutions of DIM (0.001%, 0.01%, 0.1%, 1%) in petrolatum were used in the drug patch test. DIM 0.001% was negative, but all the higher concentrations of DIM were strongly positive. Drug patch testing with DIM 1% in petrolatum was performed in 5 healthy controls, which were all negative after 48 hours, 72 hours, and 7 days. A lymphocyte transformation test, measuring the DIM-specific T-cell proliferation,⁷ was negative.

After the positive drug patch test for the DIM complex and the negative drug patch test for naproxen, the patient also received an oral challenge with naproxen 220 mg for 3 days that was negative.

CONCLUSION

The clinical picture of many pustules on an erythematous background did lead us to consider acute generalized exanthematous pustulosis (AGEP) as the diagnosis. However, the long time interval between the start of drug intake and the

reaction and the cutaneous manifestations of edema and pustules accompanied by typical hematological abnormalities and visceral organ involvement as well as delayed resolution support the diagnosis of DRESS rather than AGEP or DRESS/AGEP overlap.^{8,9} Using the criteria of the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR)³ our patient was diagnosed with definite DRESS (score 6).

This is the first case report that shows that the over-the-counter available dietary supplement DIM, which is also a potential chemopreventive agent and investigational drug, is not completely harmless but can cause DRESS, a severe drug reaction. Drug causality could safely be assessed in our case by the drug patch test. This case report stresses the importance of obtaining a complete drug history, including information about the use of dietary supplements.

^aDepartment of Dermatology/Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

^bLaboratory of Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

^cDepartment of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication May 25, 2015; revised July 5, 2015; accepted for publication July 10, 2015.

Available online August 19, 2015.

Corresponding author: Thuy-My Le, MD, PhD, Department of Dermatology/Allergology (G02.124), University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: t.t.m.le-2@umcutrecht.nl.

2213-2198

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2015.07.007>

REFERENCES

- Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg* 1996;15:250-7.
- Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. *Arch Dermatol* 2010;146:1373-9.
- Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-11.
- Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, 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;169:1071-80.
- Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. *Pharmacol Res* 2007;55:224-36.
- Reed GA, Sunega JM, Sullivan DK, Gray JC, Mayo MS, Crowell JA, et al. Single-dose pharmacokinetics and tolerability of absorption-enhanced 3,3'-diindolylmethane in healthy subjects. *Cancer Epidemiol Biomarkers Prev* 2008;17:2619-24.
- Tsuge I, Okumura A, Kondo Y, Itomi S, Kakami M, Kawamura M, et al. Allergen-specific T-cell response in patients with phenytoin hypersensitivity: simultaneous analysis of proliferation and cytokine production by carboxy-fluorescein succinimidyl ester (CFSE) dilution assay. *Allergol Int* 2007;56:149-55.
- Sidoroff A, Halevy S, Bavinck JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction pattern. *J Cutan Pathol* 2001;28:113-9.
- Bouvesse S, Valeyrie-Allanore L, Ortonne N, Konstantinou MP, Kardaun SH, Bagot M, et al. Toxic epidermal necrolysis, DRESS, AGEP: do overlap cases exist? *Orphanet J Rare Dis* 2012;7:72.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.