Modafinil-induced drug reaction with eosinophilia and systemic symptoms syndrome

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Key words: DRESS; drug-induced hypersensitivity syndrome; drug reaction; drug reaction with eosinophilia and systemic symptoms; modafinil; severe drug eruption.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe and potentially life-threatening adverse drug reaction that is associated with a cutaneous eruption and multiorgan dysfunction.[1] The syndrome occurs most frequently with anticonvulsants, sulfonamides, and nonsteroidal anti-inflammatory drugs.[1] We present a case of DRESS syndrome associated with the initiation of modafinil in a critically ill patient. Though a single case of DRESS syndrome was reported in postmarket studies of modafinil following Food and Drug Administration approval, there is a paucity of case reports describing this particular drug association in the literature.[2]

Abbreviations used:

DRESS:	drug reaction with eosinophilia and systemic symptoms
RegiSCAR:	European Registry of Severe Cutaneous Adverse Reactions

CASE SYNOPSIS

A 28-year-old male with a past medical history of anoxic encephalopathy resulting in a persistent vegetative state was admitted to the intensive care unit with hypernatremia, acute kidney injury, and gastrostomy feeding tube malfunction. His feeding tube was replaced, and his kidney function improved with intravenous fluids. He was started on modafinil (200 mg daily), which has been shown to enhance cognition in chronically encephalopathic patients.[3]

Approximately 3 weeks later, the patient developed a diffuse erythematous rash containing macules and vesicles on the trunk, neck, upper extremities, and proximal lower extremities (Fig 1). This rash was exaggerated in the intertriginous regions (Fig 1) and associated with a fever of 40.3 °C, mild facial edema, and respiratory decompensation. No lymphadenopathy, bullae, erosions, target lesions, or mucosal lesions were observed. Laboratory studies found isolated eosinophilia (0.80 $\times$ $10^3/\mu$L) without leukocytosis (white cell count, 7.76 $\times$ $10^3/\mu$L) and elevations in serum creatinine (from 1.25 to 1.60 mg/dL) and liver enzymes (aspartate aminotransferase level, 131 U/L; alanine aminotransferase level, 96 U/L). No atypical lymphocytes were seen on peripheral blood smear. Serology results for hepatitis A, B, and C were negative. Polymerase chain reaction tests for Epstein-Barr virus, cytomegalovirus, and herpes simplex virus were negative. A chest radiograph demonstrated new diffuse bilateral interstitial infiltrates. One of two sets of blood cultures was positive for *Staphylococcus epidermidis*, which likely represented a contaminant. Urine cultures were positive for *Proteus mirabilis* (50,000-99,000 CFU/mL), but

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Funding sources: None.

IRB approval status: Not applicable.

Patient consent: Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that all patients gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

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JAAD Case Reports 2022;27:131-3.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.07.024

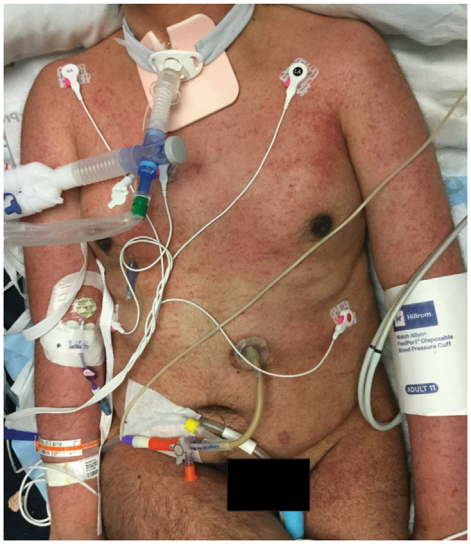

Fig 1. DRESS syndrome. Diffuse erythematous macules and vesicles on the neck, chest, abdomen, upper extremities, and proximal lower extremities. The rash is more confluent in intertriginous regions. The patient is mechanically ventilated with a chronic tracheostomy, gastrostomy feeding tube, and external catheter in place.

this likely represented colonization rather than a true urinary tract infection.

According to the Naranjo Adverse Drug Reaction Probability Scale (score = 7), the cutaneous reaction was probably drug induced given that it occurred after administration of the drug, followed a recognized response to the suspected drug, improved with withdrawal of the drug, and could not be attributed to another clinical cause.[4] Findings were consistent with a diagnosis of definite DRESS syndrome per the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria.[5] Modafinil was stopped, and the patient was initiated on 60 mg of oral prednisone daily. Rash, liver dysfunction, pulmonary dysfunction, acute kidney injury, and hypereosinophilia resolved over the next 3 weeks, and prednisone was gradually tapered.

DISCUSSION

Symptoms of DRESS syndrome typically begin 2 to 6 weeks after administration of a causative agent.[1] In this case, rash and fever developed approximately 3 weeks after the initiation of modafinil. Although the patient received multiple medications—including antibiotics, vasopressors, insulin, furosemide, and amantadine—during his hospitalization, modafinil was the only new medication that was initiated in the 2- to 6-week window before symptom onset.

Cutaneous manifestations of DRESS syndrome usually consist of a morbilliform rash with macules and papules that begin in the face and spread cephalocaudally.[1] However, pustules, vesicles, and bullae may also be seen.[1,6] Patients may develop facial edema and internal organ involvement, most commonly seen in the hepatobiliary, renal, and hematologic systems.[1,6] In this case, the patient developed abnormal liver function tests, an acute kidney injury, and bilateral pulmonary infiltrates that resolved after discontinuation of modafinil and treatment with systemic steroids.

DRESS syndrome is often diagnosed clinically, as histology can be nonspecific. Given that many symptoms of DRESS syndrome can be seen with systemic infections, a thorough infectious workup must be completed. The RegiSCAR has established diagnostic criteria to determine the likelihood of DRESS syndrome.[5] In this case, our clinical diagnosis was supported by a RegiSCAR score of 6 suggesting definite DRESS syndrome: fever $\geq$38.5 °C (0), no lymphadenopathy (0), no atypical lymphocytes (0), eosinophilia (+1), rash affecting greater than 50% body surface area (+1), facial edema and scaling (+1), no biopsy (0), internal organ involvement (+2), disease duration $\geq$15 days (0), and 3 or more negative biologic investigations (+1).[5]

Patients with DRESS syndrome often warrant hospitalization because it is associated with a 10% mortality rate.[1,7] The suspected causative medication should be withdrawn immediately. Treatment of mild cases involves supportive care with emollients, topical steroids, and fluid replacement. Treatment of DRESS syndrome with multi-organ involvement often requires initiation of systemic corticosteroids.[7] Corticosteroids should be tapered slowly (over 4-6 weeks), as there is a risk of relapse with rapid tapering.[7]

Modafinil is a wake-promoting agent that was initially approved as a treatment for excessive somnolence associated with narcolepsy, obstructive sleep apnea, and shift work sleep disorder.[8] Its exact mechanism is unclear, but it has been shown to inhibit γ-aminobutyric acid mediated neurotransmission[9] and increase dopamine in the brain by inhibiting dopamine transporters.[10] Modafinil has also been used off-label for the treatment of depression, attention-deficit/hyperactivity disorder, multiple sclerosis, Parkinson disease, cancer-related fatigue, and prolonged encephalopathy in patients with traumatic brain injury or stroke.[3,9]

According to modafinil clinical trial data in 934 patients, the most commonly reported adverse effects were headache (34%), nausea (11%), nervousness (7%), rhinitis (7%), back pain (6%), and diarrhea

(6%).[8] A single case of DRESS syndrome was reported in a 15-year-old patient who began to take modafinil for attention-deficit/hyperactivity disorder during postmarket surveillance of modafinil.[2] Overall, few cases of severe cutaneous events have been reported with modafinil use, but there have been isolated cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme.[2]

This case demonstrates that DRESS syndrome is a rare potential adverse effect of modafinil. Clinicians should be cognizant of this drug reaction associated with the use of modafinil, especially because there is an increasing trend of off-label use for depression, attention-deficit/hyperactivity disorder, and Parkinson disease.

Conflicts of interest

None disclosed.

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