# Strontium citrate associated drug reaction with eosinophilia and systemic symptoms syndrome with granulomatous dermatitis

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## INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic, type IV, delayed hypersensitivity drug reaction characterized by fever, rash, lymphadenopathy, hematologic abnormalities, and multiorgan involvement.[1] DRESS has been described secondary to a variety of drugs, most commonly allopurinol and sulfasalazine.[1] Previously unreported drug reactions are being identified as an increasing number of patients take vitamins and over-the-counter supplements. We report a novel drug reaction leading to DRESS with subsequent granulomatous dermatitis as a result of taking strontium citrate, which is an over-the-counter supplement.

*Abbreviation used:*

DRESS: drug reaction with eosinophilia and systemic symptoms

## CASE REPORT

A 51-year-old woman presented to the clinic with a one-week history of eruptions involving her trunk and extremities and accompanied by oral erosions. Her outpatient medications included levothyroxine, sumatriptan, topiramate, trazodone, and alprazolam. She also reported taking one supplement called "elderberry." On initial examination, she was found to have mucosal erosions as well as scattered diffuse, erythematous, and edematous papules. She was empirically treated with topical corticosteroids and valacyclovir hydrochloride (Valtrex). Despite these therapies, the patient's symptoms progressively worsened, and she developed headaches, decreased appetite, malaise, fever, lymphadenopathy, and weakness. She presented to the emergency room and a skin biopsy was performed. Her laboratory values were notable for an aspartate aminotransferase of 121 U/L (reference range, 10-35 U/L), alanine aminotransferase of 188 U/L (reference range, 10-35 U/L), Creatinine of 1.06 mg/dL (reference range, 0.51-0.95 mg/dL), hematocrit of 47.3% (reference range, 34%-44%), and C-reactive protein of 134.3 mg/L (reference value, $\leq 5$ mg/L). Workup included an extensive viral panel, blood cultures, and antibody testing, which were all negative. On day 2 of admission, she began to develop confluent plaques on all extremities (Fig 1, *A*), papules and plaques with an overlying pseudo-vesicular appearance, and lesions on the back studded with scattered pustules (Fig 1, *B*). The patient was noted to have progressive facial edema (Fig 1, *C*). Liver function tests continued to trend upwards, and she developed leukocytosis at $15.87 \times 10^9$ cells/L (reference range, $4\text{-}11 \times 10^9$ cells/L) and eosinophilia at $1.25 \times 10^9$ cells/L (reference range, 0.00-

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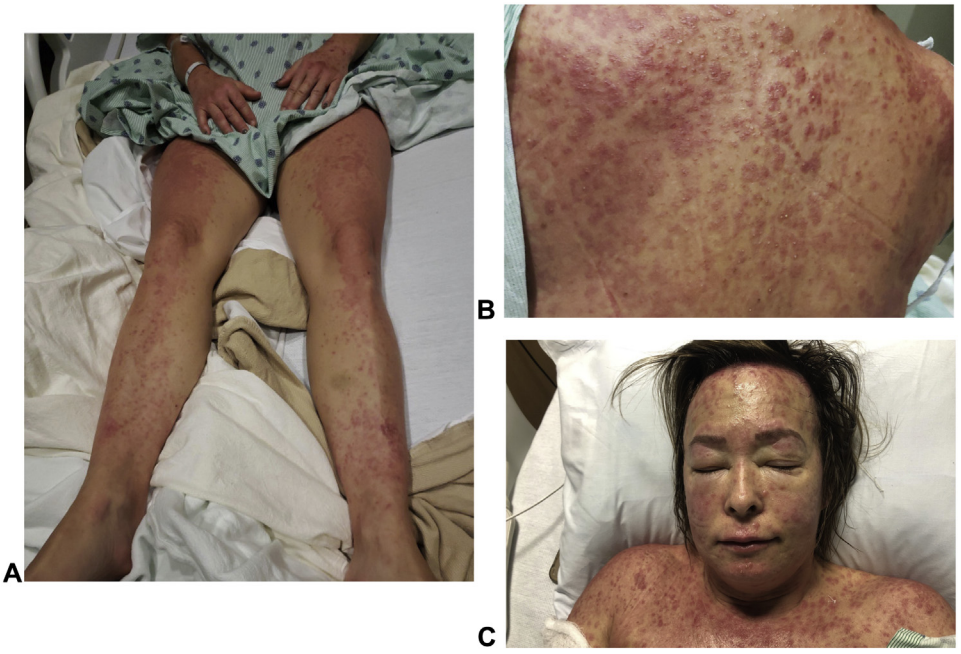


**Fig 1.** Clinical photographs of the patient's DRESS disease course. **A**, Image demonstrating hands and legs with erythematous papules coalescing into confluent plaques. **B**, Image demonstrating back studded with scattered pustules and an overlying pseudo-vesicular, juicy appearance on top of papules and plaques. **C**, Image of the face and upper chest with scattered erythematous papules coalescing into small plaques with the evidence of significant facial edema.

$0.70 \times 10^9$ cells/L). At this point, she recalled taking 3 other supplements: Sleepwell, AlgaeCal Plus, and strontium citrate. She had been taking the first 2 supplements for several months, but the latter medication was self-initiated 6 weeks prior to the presentation at a dosage of 1.36 g daily. The rash morphology, antecedent drug history, fever, eosinophilia, elevated liver enzymes, and a biopsy favoring a drug reaction (Fig 2, *A*), as well as a Registry of Severe Cutaneous Adverse Reactions score of 5, were all consistent with a diagnosis of DRESS. Strontium citrate was thought to be the most likely causative agent, given the timing of strontium supplementation as well as notable studies in Europe with DRESS developing secondary to strontium ranelate administration.[1] She was started on intravenous methylprednisolone and skin lesions subsided upon withdrawal of strontium citrate. Two weeks after discharge, the patient developed ocular changes with a left lateral scotoma and a new rash on her trunk, which appeared as numerous skin-colored papules. Biopsy revealed discrete areas of palisading histiocytes with perivascular lymphocytes consistent with granulomas (Fig 2, *B*). In the context of her clinical presentation, she was diagnosed with granulomatous dermatitis associated with DRESS. An ophthalmologist evaluated the patient and diagnosed her with glaucoma and pattern macular dystrophy of the left eye greater than the right, secondary to the drug reaction. It is unclear whether strontium citrate was also responsible for her new-onset ocular findings, both of which are not typically associated with DRESS or granulomatous dermatitis. Her granulomatous reaction resolved over the following month without treatment, but the patient remains under ophthalmologic treatment.

## DISCUSSION

Strontium is a naturally occurring alkaline earth metal found in soil. Strontium ranelate has been recommended for postmenopausal women with a bone mineral density T-score of -3.0 or lower and as a treatment for osteoporosis due to its dual action of reducing bone resorption and increasing bone formation.[2] The recommended oral dose is 2 g once daily.[2] A range of adverse reactions has been reported, 26% of which are cutaneous.[3] In 2014, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommended that strontium ranelate no longer be used due to safety concerns,[4] and the manufacturer ceased distribution of this product in 2017.[5]

A supplement of an alternative strontium salt, called strontium citrate, which is made synthetically

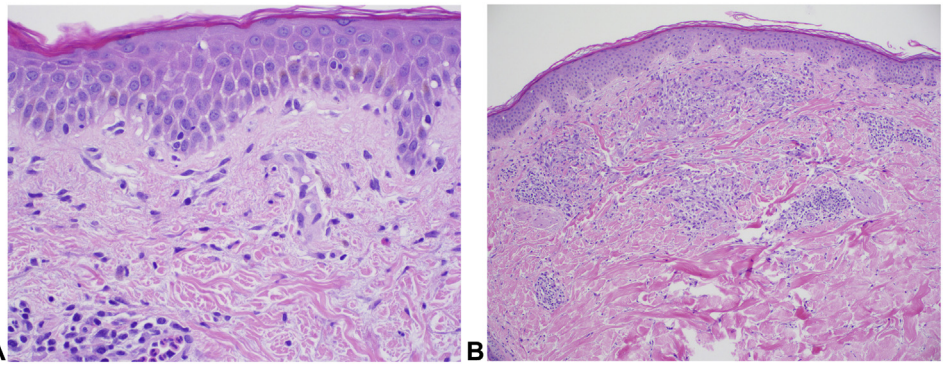

**Fig 2.** **A**, A punch biopsy from the right back demonstrating superficial perivascular dermatitis consistent with drug eruption. There is a superficial perivascular and interstitial infiltrate of lymphocytes and a few histiocytes, along with eosinophils. Some lymphocytes are enlarged and show focal atypia. There is also spongiosis and focal vacuolar degeneration of the basement membrane. **B**, A punch biopsy from the left shoulder demonstrating infiltrates of perivascular lymphocytes and dermal histiocytes forming palisaded granulomas.(**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×400; **B**, ×100.)

from strontium minerals and citrate, is readily available in the United States. It has been marketed as a naturally occurring supplement for increasing bone density. Rather than supplementing the diet, however, patients are provided pharmacologic doses. One unit of supplement provides 680 mg of strontium citrate and instructions recommend taking 2 capsules per day, which is much more than the natural dietary intake of 2-4 mg/day and is almost equivalent to the concentration of prescribed strontium ranelate.[6]

Beginning in 2007, reports of hypersensitivity syndromes related to strontium ranelate, such as DRESS, were documented.[1] Strontium ranelate has been reported to induce 325 hypersensitivity events with cutaneous eruptions, of which DRESS was identified in 47 cases.[1]

In addition to DRESS, the intake of strontium citrate likely led to granulomatous dermatitis in our patient. The association between granulomatous dermatitis and DRESS has been demonstrated in prior studies.[7,8] There have also been reports of DRESS associated with systemic granulomatous inflammation.[9] Interestingly, one prior report described a patient who developed an interstitial granulomatous drug reaction after strontium ranelate.[10] Given these findings, granulomatous dermatitis should also be considered by dermatologists when presented with patients taking strontium citrate with or without concomitant DRESS.

In conclusion, an alternative formulation of strontium ranelate, strontium citrate, should be added to the list of culprits leading to DRESS syndrome. While strontium has been reported to be associated with DRESS and, in one case report, a granulomatous drug reaction, there are no reports of patients who have experienced both of these rashes concomitantly as seen in the patient described here. The coexistence of granulomatous dermatitis in the setting of DRESS has been reported in a few instances in the literature, and although uncommon, this association is noteworthy. It is necessary to be aware of this or other potential cutaneous adverse reactions in patients taking strontium citrate.

### Conflicts of interest

None disclosed.

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