# Cutaneous pseudolymphomatous drug eruption secondary to supplemental flaxseed oil

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***Key words:*** cutaneous T-cell lymphoma; drug eruption; mycosis fungoides; pseudolymphoma.

## INTRODUCTION

Cutaneous pseudolymphoma is nearly identical morphologically and histologically to cutaneous lymphoma. Differentiating between the two requires an appropriate index of suspicion and a thorough history. Misdiagnosis of a benign condition as malignant may result in unnecessary treatment and associated adverse events related to those therapies. A thorough history along with a methodic medication reconciliation is crucial to ruling out possible contributors to pseudolymphomatous drug eruptions. Identification and removal of the offending agent can lead to rapid resolution of the condition.

*Abbreviation used:*

MF: mycosis fungoides

## CASE REPORT

A 51-year-old woman presented with a 6-month history of a pruritic eruption involving her trunk and upper extremities and recalcitrant to topical triamcinolone ointment. She took no prescription medications but reported beginning the flaxseed oil a few weeks before the eruption onset. On examination, there were erythematous patches and thin plaques involving the trunk and upper extremities. A skin biopsy showed an atypical superficial interstitial lymphocytic infiltrate extending into the reticular dermis with lymphocyte exocytosis of small lymphocytes, some of which appeared to have clear halos. The lymphocytes stained with antibodies against CD3, and the CD4:CD8 ratio of the epidermal lymphocytes was approximately 1:4. The biopsy was suspicious for $CD8^+$ cutaneous T-cell lymphoma, mycosis fungoides (MFs)—type (Fig 1). At the initial visit with a cutaneous oncology specialist, she had been off the supplements for 3 weeks, including a probiotic, methylsulfonylmethane, vitamin C, shark cartilage, calcium, vitamin D, and flaxseed oil, with slight improvement of her skin findings (Fig 2). She had no systemic symptoms, no new foreign agents (ie, tattoos, vaccinations, and piercings) or sick contacts, and no history of travel. The clinicopathologic differential diagnosis included MFs and cutaneous pseudolymphoma. It was recommended that she continue to withhold the supplements and to apply a medium-potency topical steroid ointment on affected areas twice daily for 2 weeks and return to the clinic in 2 months for possible further molecular testing. At the follow-up appointment, she had complete resolution of the rash, despite prior recalcitrance to topical steroids. She gradually reintroduced all supplements except for flaxseed oil, without recrudescence of the eruption. She was clear for at least 2 years post discontinuation of the flaxseed oil.

## DISCUSSION

Cutaneous lymphoma and pseudolymphoma are often difficult to differentiate. Cutaneous

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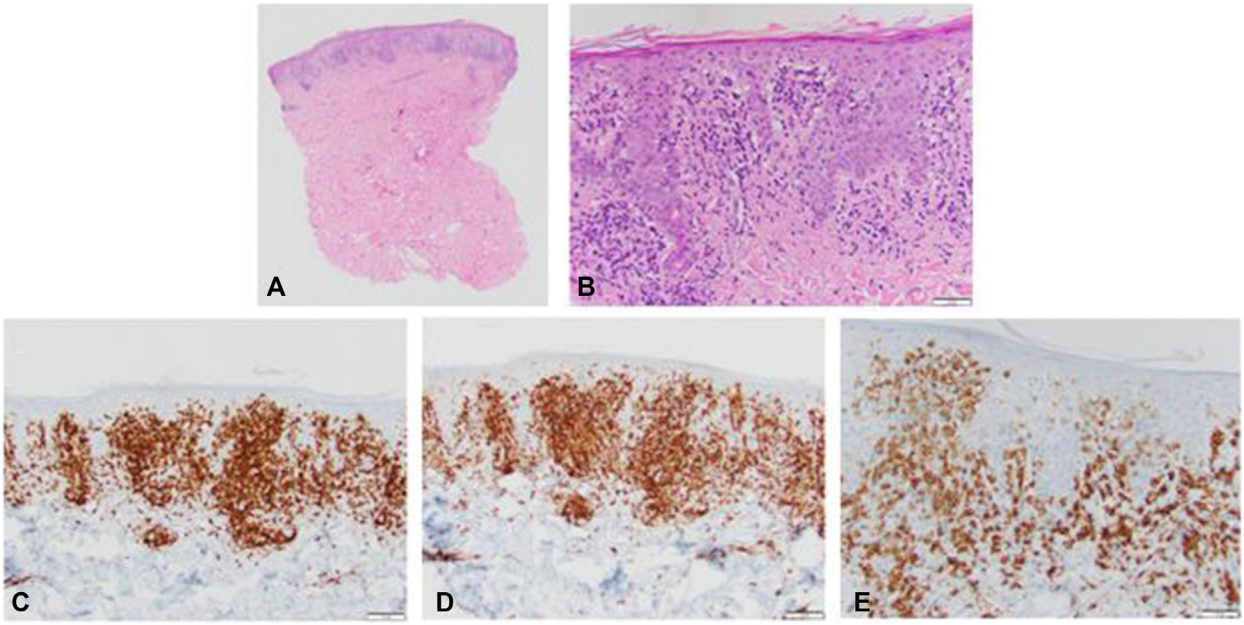


**Fig 1.** Scanning magnification of a hematoxylin-eosin–stained preparation revealed a superficial infiltrate, and higher magnification revealed mild vacuolar interface dermatitis with mild lymphocyte hyperchromasia, enlargement, and exocytosis. Immunostains revealed that the infiltrate was positive for CD3, and many small dermal lymphocytes and dendritic epidermal cells were $CD4^{+}$, whereas CD8 staining highlighted the larger epidermotropic cells of interest. (Original magnifications: **A,** ×2; **B,** ×20; **C,** ×10; **D,** ×10; **E,** ×20.)

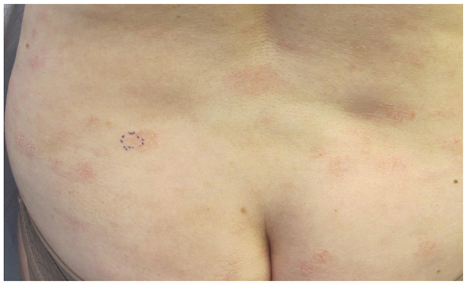

**Fig 2.** Multiple pink patches on the lower portion of the back and the buttocks.

lymphoma is usually either B-cell or T-cell predominant, and is further divided into various subtypes. With regard to cutaneous T-cell lymphoma, MFs is the most prevalent subtype.[1] MFs classically presents as well-marginated, mildly erythematous, and slightly scaling patches or thin plaques in typically doubly-clothed areas of the body, often involving the breasts, buttocks, lower part of the trunk, and groin. The patches may progress to form more deeply infiltrative plaques, tumors, and ulcerations.[2] The 10-year survival rate of early-stage disease is similar to that of the general population but is less favorable with erythrodermic, lymphatic, and visceral involvement, reaching <25% for stage IVB disease.[2,3] Diagnosis may be delayed because early skin biopsies frequently lack disease-defining features.[4] The classic histology of MFs reveals epidermotropism of atypical lymphocytes in areas without spongiosis and papillary dermal fibrosis.[4] The lymphocytes have clear halos and form aggregates within the epidermis. CD4-predominant T-cell epidermal infiltrates are more common; however, a minority of the cases display a CD8-predominant phenotype. Several studies have determined that this phenotype has no prognostic significance.[5,6] Identification of positive T-cell clonality on T-cell gene rearrangement studies strengthens a diagnosis of cutaneous T-cell lymphoma in combination with other findings but is not fully specific for the diagnosis, as inflammatory conditions may occasionally also have clonal T-cell rearrangements.[2,4] Currently, treatment for the early stages of MFs is typically skin-directed, including phototherapy, radiation therapy, and topical medications (ie, topical corticosteroids, mechlorethamine, and bexarotene).[1] Each of these is associated with specific adverse sequelae, as are systemic treatments with small-molecule agents and biologics for recalcitrant or progressing disease.[1,7]

Cutaneous pseudolymphoma encompasses a group of benign skin diseases characterized by

lymphoproliferative processes that clinically and histologically simulate cutaneous lymphomas.[8] Reported causes include infection, vaccinations, allergens, insect bites, drugs, and photosensitivity.[8] All cases require careful clinical-pathologic correlation to rule out lymphoma, and many require additional investigations, including serologic tests, gene rearrangement studies, flow cytometry of skin tissue, and patch testing.[9] Atypical morphology or peripheral distribution may raise suspicion, although clinical findings are broad.[8] Histologic analysis may reveal superficial infiltrate patterns, increased lymphocyte size, and immunophenotypes that may mimic lymphoma. The presence of eosinophils or mixed histologic patterns, including spongiosis and interface dermatitis in the setting of an aberrant immunophenotype, raises the suspicion of a drug eruption. However, histologic and molecular findings should always be interpreted within a clinical context. As in the case of our patient, pseudolymphomatous conditions must be followed over time after withdrawal of the offending agent. Reintroduction of the suspected offending agent has potential risk and ethical considerations.

Differentiating a lymphomatous process from a drug-related pseudolymphoma requires a careful and thorough physical examination, which may indicate a morphology or distribution that is not classic for MFs. Our patient's eruption began soon after starting flaxseed oil supplementation, and the remaining supplements were eliminated as likely culprits, given her chronologic history and their reintroduction without relapse. Various medications have been reported to cause pseudolymphomatous drug eruptions, including antiarrhythmics, antipsychotics, antihypertensives, and anticonvulsants.[10] There are only limited reports of supplement-induced pseudolymphoma, and we were not able to find other cases involving flaxseed oil. In some cases, skin findings can quickly regress with removal of these offending agents; however, in others, autoinflammatory processes induced by the inflammation associated with the drug reaction can be attenuated with short-term steroid therapy. In our case, the patient discontinued the flaxseed oil supplement, which, fortunately, this action combined with a short course of topical steroids, was curative.

Pseudolymphomatous drug eruption should be considered in patients who present with clinical and pathologic findings suggestive of cutaneous T-cell lymphoma. A misdiagnosis of malignancy can lead to overtreatment resulting in adverse side effects and high costs. Additionally, a cancer diagnosis may unnecessarily impose a significant psychologic burden on the patient.

**Conflicts of interest**

None disclosed.

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