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Acute Generalized Exanthematous Pustulosis Due to Milk Thistle (*Silybum marianum*) Tea[☆]

Pustulosis exantemática generalizada aguda debida a una infusión de cardo mariano (*Silybum marianum*)

To the Editor:

Acute generalized exanthematous pustulosis (AGEP) is a rare disease that has been linked to certain drugs, such as antibiotics, antifungal agents, anticonvulsants, and antihypertensive agents.¹⁻³ Other possible triggers that have been described include infection, pregnancy, allergens, spider bites, iodinated contrast media, herbal medicinal products, and tumors.² In some cases, however, the causative agent cannot be identified.¹

Several hypotheses that have been proposed to explain the pathogenesis of this skin reaction involve T lymphocytes and cytokines and posit that they are responsible for the characteristic neutrophilia and the aggregates of neutrophils in the histological picture of AGEP. It is recognized that previous sensitization, including contact sensitization, could explain some of these drug eruptions, and patch testing is positive in up to 80% of drug-related cases.⁴

A 45-year-old man with hyperuricemia on treatment with allopurinol for the previous 3 years consulted for an acute disorder that had started on the trunk 48 hours earlier and had spread to the face and limbs; he also reported fever and general malaise. Physical examination revealed erythema and edema of the skin of the face, trunk, and limbs—including the skinfolds and the palms—associated with multiple nonfollicular pustules (Fig. 1). There were also lesions on the oral mucosa and erosions on the lips. He did not report a history of infection and there had been no changes in the dose of his usual medication or new treatments added in the previous 3 months. However, he did remember taking milk-thistle infusions for a week before the onset of symptoms. The preparation, bought in a herbalist shop, contained dried seeds and was used by the patient to prevent dyspepsia. Histopathology of a lesion showed intraepidermal pustules, with edema of the papillary dermis and a predominantly neutrophilic perivascular inflammatory infiltrate. No acanthosis or papillomatosis was observed. The results of additional tests were as follows: white cell count, 16 500/ μ L (normal range, 4000-11 000/ μ L) (neutrophils,

10 000/ μ L [normal range, 2000-7500/ μ L]; eosinophils, 600/ μ L [normal range, 40-400/ μ L]; creatinine, 2.2 mg/dL (normal value, <1.1 mg/dL), and C-reactive protein, 256 mg/L (normal value, <12 mg/L). Culture of the pustules and blood cultures were negative. Serology for hepatitis B and C viruses, Epstein-Barr virus, and cytomegalovirus was negative. The patient did not recall having taken milk-thistle infusions previously, had no known drug allergies, and did not report any personal or family history of psoriasis. The findings of the medical history and of the additional tests were consistent with the clinical suspicion of acute generalized exanthematous pustulosis. Furthermore, the criteria proposed by Roujeau¹ were satisfied and, based on the validation scale proposed by the study group of the European study of severe cutaneous adverse reactions (EuroSCAR),² a definitive diagnosis of AGEP could be made. Treatment was started with oral prednisone at a dose of 0.5 mg/kg in a tapering regimen, in addition to emollients and fluid support. The clinical course was favorable, with resolution of the lesions and normalization of the complete blood count and renal function within 15 days. Patch testing was performed with the standard European series (Marti i Tor, Spain) 8 weeks after resolution of the condition. In addition, the hospital pharmacy prepared a 10% aqueous solution of the product supplied by the patient, which contained dried milk-thistle seeds. The results at 48 and 96 hours were positive (++) with an eczematous reaction at the site of application of the milk-thistle preparation. Other allergens in the patch tests were negative at the same time intervals. The results obtained with the same milk-thistle preparation in 10 control cases were negative. The patient has presented no further episodes after a year of follow-up.



Figure 1 Multiple nonfollicular pustules on an erythematous, edematous base.

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Milk thistle (*Silybum marianum*) is a natural product that has been known for a long time and has been used for the treatment and prevention of diseases of the liver and gallbladder, as well as in some types of cancer.⁵ In traditional medicine, it has been used to treat hormonal alterations in women, digestive tract problems, acne, and psoriasis. It has also been claimed that milk thistle detoxifies environmental toxins, alcohol, and copious meals. The active substance is a flavonoid complex called silymarin, which has anti-inflammatory properties, regulating certain mediators such as tumor necrosis factor and interleukins 1 and 6. In some European countries, products are available that contain known and established doses of the active substance (between 70% and 80% silymarin). However, the doses and additives are frequently unclear in many preparations obtained in health-food and herbalist shops, where milk thistle is sold in the form of capsules and tablets or as leaves and seeds that are used to prepare infusions. The active substance, silymarin, reduces the activity of the cytochrome P450 complex and may affect the clearance of some drugs, although no interactions have been reported to date. Silymarin is generally considered to be safe and well tolerated, and serious adverse effects are rare. Gastrointestinal discomfort and diarrhea have been reported,⁶ as well as skin manifestations, such as itching, rash, eczema, and anaphylaxis.^{5,6} After a review of the currently available literature, we believe this to be the first reported case of acute generalized exanthematous pustulosis due to milk thistle. However, we cannot be certain that the causative agent was the milk thistle because it could also have been one of the additives, which were not listed on the packet. Nor was it possible to exclude an interaction with allopurinol.

Although there is widespread use of herbal medicines in present-day society, the reporting of cutaneous adverse effects is not common, although cases of allergic contact dermatitis, Stevens-Johnson syndrome, photodermatoses, pellagra, and angioedema have been described. We have found 3 articles that describe the association of AGEPS with herbal medicines.⁷⁻⁹ The first report makes no reference to any specific plant, as the composition of the product was unknown (products bought in health-food and herbalist shops and at street stalls sometimes lack labels or the labels do not list all of the components and concentrations).⁷ The second was a case of AGEPS in a patient who took a medicinal product that contained only *Ginkgo biloba*,⁸ and the third article described a case related to the ingestion of chicken cooked with *Rhus*.⁹ As patch testing was not possible in any of the above cases, diagnosis was based on the temporal relationship and the fact that the problem

resolved and did not recur after withdrawal of the causative agent.

We believe it is important to report this case because it illustrates the relevance of herbal medicines, often considered innocuous, in the appearance of skin lesions. As dermatologists, we should consider this possibility and take an appropriate medical history as, like health professionals, the patients do not usually take these products into account and fail to report their use.

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