



Figure 1. Patch testing to DCP after repeat sensitization. The right side represents the second round of patch testing from 0.0001% (marked as 1) to 1% (marked as 7) DCP. The left side represents previously applied patch testing of the same dilution series that demonstrated recall reaction with remote application.

Recurrent dermatitis to nickel, gold,¹ or chromate² at previously sensitized sites following re-exposure to new (nonadjacent) sites has been reported. Recurrent dermatitis to neomycin³ and nickel⁴ at previously sensitized areas after patch testing at distant sites has also been described. Although “recall reactions” with synthetic allergens may be encountered on primary sensitized areas, our case is the first to report a recall reaction at a remote applied patch test site. The mechanism for these reactions is unclear. We hypothesize that effector memory T cells persist at the original site of sensitization, and these cells are reactivated by resensitization at a remote site.⁵ Conversely, it could be the allergen that persists at the original site of sensitization, with allergic dermatitis becoming manifest; thereafter sufficient numbers of effector memory T cells populate it following re-exposure to allergen at a distant site.

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Acute Generalized Exanthematous Pustulosis Associated With Acyclovir, Confirmed by Patch Testing

To the Editor:

Acyclovir, a commonly prescribed antiviral drug, has rarely been implicated in severe cutaneous adverse drug reactions.^{1,2}

A 53-year-old man with a herpetic retinitis was being treated with systemic acyclovir and methylprednisolone. Previously, he had also received antibiotics with no adverse effects. Three weeks after starting acyclovir (intravenously during 2 weeks and orally for 7 days), he developed a severe febrile eruption consisting of generalized erythema with numerous small pustules that initially appeared on major intertriginous areas (Fig. 1). His medical history was unremarkable, and he denied any personal or family history of psoriasis or previous use of topical acyclovir. Laboratory evaluation disclosed leukocytosis (24,400/ μ L), neutrophilia, and an elevated C-reactive protein. A skin biopsy revealed multiple subcorneal spongiform pustules filled with neutrophils and a perivascular, lymphomononuclear inflammatory infiltrate in the upper dermis. A diagnosis of acute generalized exanthematous pustulosis (AGEP) was established. Careful revision of prescription charts allowed identification of acyclovir as the probable cause, and it was replaced by foscarnet, while methylprednisolone was maintained. Complete resolution, after a desquamative phase, was achieved in less than 2 weeks.

Two months later, patch tests were performed with an extended European Baseline Series, systemic antibiotics, excipients for topical drugs, acyclovir 10% pet (Chemotechnique Diagnostics, Vellinge, Sweden), commercial creams containing acyclovir at 2% or 5%, and a commercial cream containing penciclovir at 1% (Fenivir). Also, pure acyclovir supplied by the pharmaceutical industry was

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Histopathologic specimens were reviewed by Prof Oscar Tellechea, from the Dermatopathology Unit, Hospitais da Universidade de Coimbra. Prof Artur Paiva, from the Centro de Histocompatibilidade do Centro, Coimbra performed the lymphocyte stimulation test.

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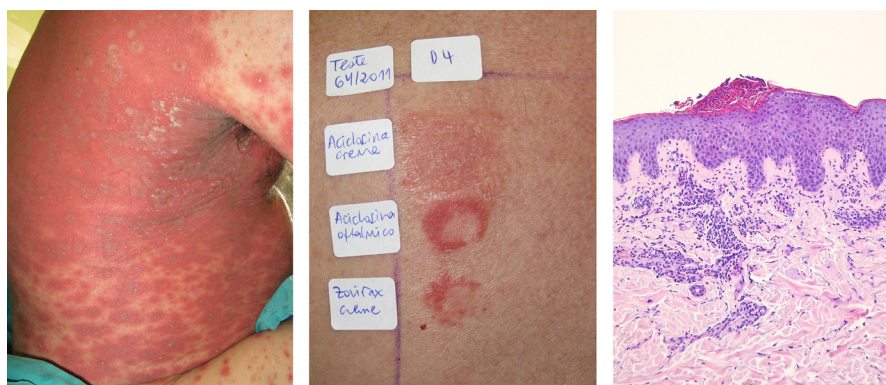


Figure 1. Acute generalized exanthematous pustulosis to acyclovir: lesions during the acute episode (left); positive patch tests with commercial topical formulations of acyclovir, Aciclosina and Zovirax, originating micropustules on an erythematous base with edge effect (center); biopsy of positive patch test (right) disclosed subcorneal pustules and a moderate inflammatory infiltrate in the upper dermis, findings consistent with AGEP.

prepared by us and tested in different vehicles (water, petrolatum, dimethyl sulfoxide, and propylene glycol) and concentrations (2%–10%). Positive reactions were obtained only with the commercial topical formulations of acyclovir (Aciclosina cream, Aciclosina ophthalmic ointment, and Zovirax cream), with infiltrated erythema and micropustules from day 2 onward (Fig. 1). A punch biopsy revealed histopathologic changes similar to those found during the acute episode (Fig. 1). Patch tests with the excipients of the creams, including propylene glycol, dimethyl sulfoxide, cetostearyl alcohol, and sodium lauryl sulfate, were negative. A lymphocyte stimulation test with pure acyclovir was negative.

Acute generalized exanthematous pustulosis is a febrile eruption usually caused by drugs. Identification of the culprit agent is of utmost importance for its successful management and can be a difficult task when patients are on multidrug regimens or when there are no previous reports of this adverse event (extrinsic imputability).

Patch tests are helpful to assess drug imputability in AGEP,^{3,4} with positive tests having already been reported with more than 20 different drugs.⁴ Because we have not found other reports of AGEP induced by acyclovir, positive patch tests were an important element to confirm causality. However, positive results were obtained only with topical commercial formulations, a limitation that has already been observed when evaluating contact dermatitis from acyclovir.⁵

Interestingly, acyclovir has been recognized as a challenging allergen, with patch tests often failing to demonstrate delayed hypersensitivity to this agent.^{3,5} Commercial creams provide enhanced penetration of acyclovir in the skin, allowing the drug to efficiently reach immunocompetent cells and may sometimes represent a useful alternative. In this setting, excipients must be tested individually to rule out other reactivities.

In the present case, patch tests reproduced the original lesional pattern, clinically and histologically, strongly supporting the specific

immunological nature of this reaction. The negative result with the lymphocyte stimulation test can be explained by the limited value of in vitro assays with certain drugs and was also observed in another case of systemic reaction to acyclovir.¹ Another interesting finding in this case was the somewhat late onset of AGEP (3 weeks), as most cases tend to manifest soon after drug intake (1–3 days). The absence of prior exposure to acyclovir and the low sensitizing potential of this drug could justify this longer interval.

In summary, we recommend patch testing to better elucidate drug participation in these eruptions and call attention to acyclovir as a potential cause of AGEP.

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