A Systemic Reaction to Patch Testing for the Evaluation of Acute Generalized Exanthematous Pustulosis

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Background: Patch tests are considered safe but adverse reactions have been reported.

Observations: A case of acute generalized exanthematous pustulosis (AGEP) provoked by a patch test with acetaminophen is described. Of special interest are the negative patch test results obtained with the offending drug. The case is discussed against the background of the putative mechanisms of AGEP and the reported systemic reactions to patch testing for AGEP.

Conclusions: To our knowledge, this is the first report in the English-language literature of a generalized AGEP-like reaction caused by patch tests carried out to determine the drug eliciting AGEP.

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all readings were negative. On day 7, however, the patient developed a symmetric vesiculopustular eruption on the trunk and extremities. Histologic examination of a skin biopsy sample from one of these lesions revealed papillary edema and perivascular infiltrates with neutrophils and eosinophils. The eruption resolved after 1 week. A patch test 1 month later using only 1% and 10% acetaminophen provoked no reaction on days 2, 4, and 7. But on day 6, the patient developed a rash similar to the one that erupted on day 7 of the previous test. That rash had resolved spontaneously by day 10. Separate patch tests with each of the other ingredients of the suspected drug were negative.

Baker and Rayan1 coined *exanthemic pustular psoriasis* in 1968 to describe and name the condition, and in 1980 Beylot et al2 proposed *pustuloses exanthematiques aigue` generalisees*. The latter prevailed, and the condition is now referred to in English as acute generalized exanthematous pustulosis (AGEP).

Drugs trigger off this relatively rare phenomenon in 90% of cases, especially antibiotics and particularly β-lactams.3 Other etiologic agents are mercury; viruses, including parvovirus B19, coxsackievirus B4 and coxsackievirus A9, Epstein-Barr virus, cytomegalovirus, hepatitis B virus; and *Mycoplasmıa pneumoniae*5-7. (Table)

Several pathogenic mechanisms of AGEP have been proposed. Britschgi et al8 suggested the involvement of T cells, which is evidenced by positive patch tests and lymphocyte transformation tests. The cell-bound drug elicits a drug-specific CD4 and CD8 immune reaction producing interleukin 8 and interleukin 5. They, in turn, cause aggregation of neutrophils and eosinophils, in addition to their cytotoxic effect on basal cells.9 Based on the positive patch test results, Moreau et al10 proposed that AGEP is a delayed type of hypersensitivity reaction. Another possible mechanism is the production of antigen-antibody complexes induced by an infection or drug that activates the complement system, which in turn causes neutrophil chemotaxis.11,12

Definitive confirmation of a certain drug as the cause of AGEP theoretically can be obtained by rechallenging the patient with the suspected drug. In view of the possible recurrence of the full-fledged eruption, patch test can serve as a substitute mimicking AGEP both clinically and histologically at the patch test site only. The rationale for using patch tests in AGEP is founded mainly on the pathogenesis of AGEP, which, as mentioned above, includes T-cell involvement and a delayed-type hypersensitivity reaction. Wolkenstein et al11 reported positive patch tests in 7 of 14 patients with AGEP; Watsky14 suggested that rates of positive patch tests may be even higher, but noted that this may reflect a publication bias. The Table summarizes the drugs reported to provoke a positive AGEP patch test.15

Although the patch test reaction in most AGEP cases is limited to the test site, there are a few reports of reactions spreading beyond this site, most of them attributed to diltiazem hydrochloride. Nishimura et al10 reported a generalized AGEP-like reaction caused by a patch test with diltiazem; Vincente-Calleja et al17 described the appearance of a diffuse pruritic eruption on the neck, abdomen, and patch test area—which resolved in a few days—after a positive patch test with diltiazem; and Wake-lin and James18 reported a positive patch test with diltiazem accompanied by a mild eczematous reaction on both forearms.

Despite the value of patch tests in the diagnosis of AGEP and the determination of the condition’s etiology, the method has drawbacks. There is no standardization for the tests whose specificity and sensitivity are yet to be determined. It is well known that sometimes, including in AGEP cases, a patch test can fail to provoke a reaction in a person who is sensitive to the substance tested. There are several reasons for these negative results, especially when the test is performed with specially prepared materials rather than standard test patches. Among the more common reasons are the different mechanisms of action of the drugs being tested, excessively low drug concentration, insufficient amount of drug applied, inappropriate vehicle, degradation of the substance, and UV irradiation of the patch test site.

Our patient experienced a cutaneous reaction after taking a medication containing acetaminophen, caffeine, phenylephrine, and chlorpheniramine. Another administration of acetaminophen severely exacerbated the cutaneous reaction, which resolved a few days after the medication was discontinued. Patch tests with the alleged culprits were deemed negative despite the appearance of tiny papules at the site of application of 1% acetaminophen, because the papules lasted only 48 hours. A test with a 10-fold-higher concentration of acetaminophen was also negative, and the results of the first test with 1% acetaminophen could not be reproduced at a later time. However, with the initial patch test containing all the ingredients of the suspected drug as well as the subsequent one containing acetaminophen alone, the patient experienced a generalized cutaneous reaction con-
sisting of symmetric vesiculopustular lesions on the trunk and extremities that resolved within a few days. On histologic examination, a skin biopsy specimen of one of the vesiculopustules exhibited some of the histological features of AGEP.

Although the patch test results were negative in our case, the reproducible generalized AGEP-like reaction following patch testing with acetaminophen, together with the histological findings, suggest an acetaminophen-induced AGEP in our patient. As mentioned above, acetaminophen has already been reported as a possible cause of AGEP.

In view of the short interval (24 hours) between administration of the offending drug and appearance of the eruption, and the similarity of that rash and the rash she experienced 3 years earlier, it can also be assumed that acetaminophen caused the earlier AGEP as well.

To our knowledge, this is the first report in the English literature of a generalized AGEP-like reaction caused by patch tests carried out to determine the culprit drug in a case of AGEP. Of special interest are the negative patch test results with the offending drug.

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REFERENCES