

Patch-Test-Induced “Flare-Up” Reactions to Neomycin at Prior Biopsy Sites

Sharon E. Jacob, Chantal Barland, and Mohamed L. ElSaie

“Recall dermatitis” classically refers to the uncommon phenomenon of chemotherapy-induced reactivation of skin damage originally induced by radiotherapy months or years earlier. We compare this condition to ectopic flare-up reactions presenting as dermatitis at existing or previous sites by an inducing agent. Enhanced sensitization of an existent allergen by patch testing is rarely described. We describe a case of a 61-year-old man’s developing localized allergic contact dermatitis at previous neomycin-treated sites following the diagnosis of neomycin sensitivity on patch testing, which we attribute to a “flare-up” phenomenon.

ALLERGIC CONTACT DERMATITIS (ACD) is the clinical result of a complex immunologic cascade. The primary inciting event is a chemical trigger (allergen) penetrating the epidermis and being captured by the dendritic cells that present antigens. These Langerhans’ cells (LHCs) then carry the allergen to the lymph node and present it to naive T cells. In turn, these activated T cells are armed with the ability to immunologically respond to the next cycle of allergen triggering.

Upon rechallenge with the same chemical, the T cells initiate the production of a proinflammatory cytokine cascade and a self-perpetuating cloning and recruitment cycle. Skin tests with antigens to which the individual is sensitized provide an indirect measure of delayed hypersensitivity. This ability to recognize and immunologically respond forms the basis for patch testing. One aspect of patch testing not often discussed is ectopic flare-up reactions of an existing or preexisting dermatitis at prior sites of sensitization, induced by the test allergen. This is considered to be a complication of patch testing.

Case Report

A 67-year-old veteran with a past medical history of dysplastic nevus syndrome and “poor healing” presented to the dermatology clinic for evaluation of a chronic thigh

dermatitis (recalcitrant to topical corticosteroid, antibiotic, and antifungal therapy) and waxing and waning eczematous reactions on his torso. According to his medical record, he had been patch-tested at the Miami Veterans’ Administration Hospital with the Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test, with a 96-hour delayed reading. He was found to have positive patch-test reactions to fragrance mix I (+), potassium dichromate (+), thimerosal (++) and neomycin (++) . The reaction to neomycin had been deemed clinically relevant as he had been repeatedly applying an over-the-counter neomycin-containing ointment to the dermatitis area on the right thigh, in addition to the prescribed topical therapeutics. Because of this, the patient was advised to discontinue the use of neomycin and to continue using his topical steroid (triamcinolone 0.1% ointment).

Eight days following patch application, the patient presented “urgently” to the clinic with a worsening of his dermatitis. On physical examination, the patient was found to have a flare-up reaction of his thigh dermatitis, an intensification of the reaction at the neomycin patch-test site, and a peculiar widespread eruption of erythematous circular indurated plaques with ill-defined borders on the back, chest, and arms (Fig 1). Of note, all of the dermatitic “circles” corresponded to prior biopsy sites (which ranged in age from 2 months to 2 years).

Upon further questioning of the patient, it became apparent that he had previously treated all his biopsy sites with neomycin-based ointments, and he disclosed that he had had difficulty healing after these biopsies. Notably, these sites were the same locations of the torso eczema with which he had originally presented. We attributed the poor healing to the development of localized ACD from neomycin at the biopsy sites, and we attributed the torso

From the Department of Dermatology and Cutaneous Surgery, University of California-San Diego, San Diego, CA, and the Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL.

Reprints not available.

DOI 10.2310/6620.2008.08023

© 2008 American Contact Dermatitis Society. All Rights Reserved.



Figure 1. Flare-up reactions showing as circular indurated plaques with ill-defined borders on the patient's back.

eczema to previous flare-up reactions associated with neomycin use on the thigh. Further supporting this, the patient's dermatitis cleared with the triamcinolone ointment when the neomycin was avoided. The patient was able to discontinue the topical steroid and remain dermatitis free. It was concluded that the patient had been experiencing systematized flare-up reactions.

Discussion

Various types of delayed reactions at sites of prior dermatitis have been reported. This phenomenon was first described more than 60 years ago in radiation oncology patients, and the term “radiation recall dermatitis” was coined to refer to inflammatory skin reactions that developed at previous irradiation sites after chemotherapy administration (e.g., actinomycin).¹ “Recall” reactions have also been seen with the concomitant use of ultraviolet radiation with antibiotics,^{2–4} analgesics,⁵ and methotrexate⁶ and with radiation and tuberculostatics.⁷ Additionally, serpiginous dermatoses along the infusion vein site have been reported with 5-fluorouracil,⁸ and dermatomal drug eruptions have occurred following the use of acyclovir.⁹

“Recall dermatitis” has been reported to occur both on first exposure to a specific trigger drug¹⁰ and after repeated doses.^{11,12} It has been reported to occur in as little as hours following intravenous administration⁵ to as long as several days,¹³ weeks,¹⁴ or even months¹⁵ following oral administration. In the literature, this rare but well-recognized phenomenon is most commonly reported to involve the skin, but it has also been seen in other sites such as the

lungs,¹⁶ esophagus,¹⁷ and vaginal mucosa.¹⁸ The etiology of “recall dermatitis” remains unclear, despite a number of theories having been proposed to explain the phenomenon.^{19–21}

In addition to the classically described “recall” reactions to medications following radiotherapy, ectopic allergic flare-up reactions also represent another important category of the immune system's ability to “recall” an event. For example, metal-associated ectopic flare-up dermatitis has been described in the literature. Schultz and colleagues described an 11-year-old boy with a pruritic abdominal and wrist dermatitis (sites of prior contact with a watchband and a belt buckle) that occurred 1 week after dental braces had been installed.²² This example illustrates the systemic nature of this flare-up reaction, as an inflammatory cutaneous eruption occurred in a presensitized individual after systemic exposure to the same compound. This may also occur with a chemically related compounds.^{23,24}

Although intensification of existing clinically relevant dermatitis is common during patch testing, reports of delayed-type hypersensitivity reactions at previous ACD sites are infrequent. This type of flare-up reaction, where dermatitis is produced from coupled stimuli consisting of previous exposure and repeat exposure on patch testing, requires further research and explanation.

In our case, the patient developed the flare-up event over the 8 days following patch testing. And in a report of a case similar to our case, El Sayed and Bazex described patch-test-induced flare-up dermatitis involving the skin-folds in a patient with a chromate allergy at sites where chromate-containing cement had induced earlier contact dermatitis. The authors believed that patch testing with chromate might have facilitated its systemic absorption, resulting in a flare-up dermatitis in the absence of cement exposure.²⁵ Similarly, Thomas and colleagues described a case of phenylephrine-associated dermatitis flare-up involving the forehead and periocular regions; these flare-up reactions developed concomitantly following patch testing (with eye drops containing phenylephrine) from which the patient had developed two previous episodes of periocular dermatitis.²⁶ Furthermore, Anderson and colleagues reported a cutaneous allergic reaction with subsequent activation of an old distant site from the iontophoretic administration of 5-fluorouracil.²⁷ Flare-up reactions at sites of previous lesions (apart from external allergen contact) can also be seen in fixed drug eruptions or may rarely be encountered as “recall dermatitis” after immunomodulatory procedures such as radiotherapy or chemotherapy.

Flare-up reactions are defined as retest allergic reactions and generally follow rechallenge with an earlier sensitizing antigen.²⁸ On the basis of guinea pig models, it was previously suggested that accelerated or augmented retest reactivity at former skin sites was possible during patch testing.²⁹ The immunologic basis for these sorts of reactions, however, is poorly established. Suggested explanations hypothesize a role for ligand expression (eg, CCL27), residual antigen, or retained immunologic cells (such as LHCs³⁰ or T-cell subsets [CCR10⁺ CD4⁺])³¹ as the source of the flare-up. Our patient, with reactions in 2-month- to 2-year-old biopsy sites (with greater intensity in the newer areas), provides evidence of a retained immunologic component. We hope that this case draws attention to the possibility of neomycin-flare up reactions induced by patch testing and that it encourages discourse and research in this important area.

References

1. D'Angio GJ, Farber S, Maddock CL. Potentiation of X-ray effects by actinomycin D. *Radiology* 1959;73:175–7.
2. Blanco J, Manzanedo L, Gutierrez MC, Fuentes M. Ultraviolet recall phenomenon following the use of ampicillin. *J Invest Allergol Clin Immunol* 2002;12:215–6.
3. Kang SK. Images in clinical medicine. Radiation recall reaction after antimicrobial therapy. *N Engl J Med* 2006;354:622.
4. Krishnan RS, Lewis AT, Kass JS, Hsu S. Ultraviolet recall-like phenomenon occurring after piperacillin, tobramycin, and ciprofloxacin therapy. *J Am Acad Dermatol* 2001;44:1045–7.
5. Lee SG, Matsuyoshi N, Ohta K, et al. Drug eruption due to Bufferin showing erythema exsudativum multiforme with a photo-recall-like phenomenon. *Eur J Dermatol* 1998;8:280–2.
6. Guzzo C, Kaidby K. Recurrent recall of sunburn by methotrexate. *Photodermatol Photoimmunol Photomed* 1995;11:55–6.
7. Extermann M, Vogt N, Dayer P, Forni M. Radiation recall in a patient with breast cancer treated for tuberculosis. *Eur J Clin Pharmacol* 1995;48:77–8.
8. Kirkup ME, Narayan S, Kennedy CT. Cutaneous recall reactions with systemic fluorouracil. *Dermatology* 2003;206:175–6.
9. Mizukawa Y, Shiohara T. Which term should be used to describe drug eruptions confined to sites of previous herpes zoster lesions, 'isotopic response' or 'recall phenomenon'? *Clin Exp Dermatol* 2004;29:323.
10. Ristic B. Radiation recall dermatitis. *Int J Dermatol* 2004;43:627–31.
11. Yeo W, Leung SF, Johnson PJ. Radiation-recall dermatitis with docetaxel: establishment of a requisite radiation threshold. *Eur J Cancer* 1997;33:698–9.
12. Stelzer KJ, Griffin TW, Koh WJ. Radiation recall skin toxicity with bleomycin in a patient with Kaposi sarcoma related to acquired immune deficiency syndrome. *Cancer* 1993;71:1322–5.
13. Cassady JR, Richter MP, Prio AJ, Jaffe N. Radiation-adriamycin interactions: preliminary clinical observations. *Cancer* 1975;36:946–9.
14. Rosen G, Tefft M, Martinez A, et al. Combination chemotherapy and radiation therapy in the treatment of metastatic osteogenic sarcoma. *Cancer* 1975;35:622–30.
15. Mayer EG, Poulter CA, Aristizabal SA. Complications of irradiation related to apparent drug potentiation by adriamycin. *Int J Radiat Oncol Biol Phys* 1976;1:1179–88.
16. Schweitzer VG, Juillard GJ, Bajada CL, Parker RG. Radiation recall dermatitis and pneumonitis in a patient treated with paclitaxel. *Cancer* 1995;76:1069–72.
17. Camidge DR, Kunkler IH. Docetaxel-induced radiations recall dermatitis and successful rechallenge without recurrence. *Clin Oncol (R Coll Radiol)* 2000;12:272–3.
18. Gabel C, Eifel PJ, Tornos C, Burke TW. Radiation recall reaction to indarubicin resulting in vaginal necrosis. *Gynecol Oncol* 1995;57:266–9.
19. Putnik K, Stadle P, Schafer C, Koelbl O. Enhanced radiation sensitivity and radiation recall dermatitis (RRD) after hypericin therapy—case report and review of literature. *Radiat Oncol* 2006;1:32.
20. Hird AE, Wilson J, Symons S, et al. Radiation recall dermatitis :case report and review of literature. *Curr Oncol* 2008;15:53–62.
21. Bokemeyer C, Lampe C, Heneka M. Paclitaxel-induced radiation recall dermatitis. *Ann Oncol* 1996;7:755–7.
22. Schultz JC, Connelly E, Glesne L, Warshaw EM. Cutaneous and oral eruption from oral exposure to nickel in dental braces. *Dermatitis* 2004;15:154–7.
23. Hamilton TK, Zug KA. Systemic contact dermatitis to raw cashew nuts in a pesto sauce. *Am J Contact Dermat* 1998;9:51–4.
24. Gehrig KA, Warshaw M. Allergic contact dermatitis to topical antibiotics: Epidemiology, responsible allergens, and management. *J Am Acad Dermatol* 2008;58:1–21.
25. El Sayed F, Bazex J. Airborne contact dermatitis from chromate in cement with recall dermatitis on patch testing. *Contact Dermatitis* 1994;30:58.
26. Thomas P, Ruff F, Przybilla B. Severe allergic contact blepharoconjunctivitis from phenylephrine in eyedrops, with corresponding T-cell hyper-responsiveness in vitro. *Contact Dermatitis* 1998;38:1:41–3.
27. Anderson LL, Welch ML, Grabski WJ. Allergic contact dermatitis and reactivation phenomenon from iontophoresis of 5 fluorouracil. *J Am Acad Dermatol* 1997;36:478–9.
28. Rustemeyer T, de Groot J, von Blomberg BM, et al. Assessment of contact allergen cross-reactivity by retesting. *Exp Dermatol* 2002;11:257–65.
29. Scheper RJ, von Blomberg M, Boerrigter GH, et al. Induction of immunological memory in the skin. Role of local T cell retention. *Clin Exp Immunol* 1983;51:141–8.
30. Jacob SE, Zapolski T. Systemic contact dermatitis. *Dermatitis* 2008;19:9–15.
31. Moed H, Boersma DM, Tensen CP, et al. Increased CCL27-CCR10 expression in allergic contact dermatitis. Implications for local skin memory. *J Pathol* 2004;204:39–46.