

Quinolone allergy?

Michael Landor, MD; Alvin Lashinsky, MD; and Jennie Waxman, MD

CHIEF COMPLAINT

A 69-year-old woman was admitted for treatment of a bullous skin eruption that progressed while she received oral corticosteroid therapy.

CASE REPORT

Two weeks prior to admission the patient developed throat soreness, fever to 103 °F and posterior cervical lymphadenopathy. Oral ciprofloxacin, 500 mg twice daily, was prescribed. While her original symptoms gradually subsided, a mild, pruritic generalized rash developed on the sixth day. Ciprofloxacin was discontinued and clarithromycin and diphenhydramine were prescribed for the pruritus. The rash progressed and three days later nausea and resting dyspnea developed. All medications were stopped and oral prednisone at a daily dose of 40 mg was started. Nevertheless, the rash continued to intensify and on day 5 of prednisone the patient was admitted for further care.

History

The patient was in good health. She denied fever; headache; nasal congestion, itching or discharge; and any respiratory or gastrointestinal symptoms, arthralgias or myalgias. She had not used medicines or other chemicals and had a completely negative review of systems. A cholecystectomy had been performed 10 years previously. An intramuscular injection of penicillin received in adolescence had been followed by diffuse angioedema.

Physical examination

The patient was obese with intact mental state. Periorbital edema was apparent. Several dozen vesicles and bullae of varying sizes covered her torso and the extensor surfaces of the limbs. There was no predilection for sun-exposed sites and the face was spared. The lesions were not grouped, they were tense, and some had an erythematous base. A single buccal vesicle was present without involvement of the lips. There were no target lesions or involvement of the dorsal or volar areas of the palms and soles. Skin ulceration, hives, wheezing, hoarseness, joint effusion, lymphadenopathy, and hepatosplenomegaly were not present. Nikolsky sign was absent. Examination was otherwise unremarkable.

Laboratory tests

A complete blood count, chemistries, antinuclear antibody, and a chest radiograph were normal. There was no eosinophilia or circulating immune complexes (Raji assay). Serum protein electrophoresis disclosed minimal polyclonal hyperglobulinemia. Antibody titers to herpes simplex type 1 and 2 were each <1:10.

QUESTIONS

What is your differential diagnosis?

1. Drug eruption
2. Erythema multiforme
3. Dermatitis herpetiformis
4. Bullous pemphigoid

DIAGNOSTIC CONSIDERATIONS

There are a number of dermatoses with vesicles and bullae.¹ Having an erythematous-bullous rash with a variety of lesional sizes, our patient could have a

form of erythema multiforme. Her age group and the possible relationship to medications should raise suspicion of bullous pemphigoid. The pruritus, the restriction of the rash to the torso and the limbs, and the failure of response to oral steroids are typical of dermatitis herpetiformis. The history of exposure to antibiotics mandates consideration of a drug eruption, even though quinolones and macrolides are not common causes of drug "allergy."

QUESTIONS

What diagnostic tests should be next?

1. Observation
2. A higher dose of corticosteroids
3. A skin biopsy
4. One week trial of gluten-free diet

Establishing a therapeutic plan on the basis of these clinical considerations may be difficult. Erythema multiforme requires no intervention other than supportive therapy. Bullous pemphigoid would require a higher dose of corticosteroids. Dermatitis herpetiformis would indicate substitution of the corticosteroids with sulfapyridine or dapsone. Drug eruption is hard to document in the absence of an available skin test for quinolones and macrolides. A skin biopsy with direct immunostaining is the diagnostic test of choice.

Microscopic examination of a perilesional skin biopsy disclosed papillary abscesses without separation from the epidermis, and deep dermal infiltrates composed of neutrophils, scattered plasma cells, and lymphocytes in association with leukocytoclastic vasculitis (Fig 1). Epidermal abnormalities were not present. Immunoperoxidase stain was negative for IgA.

From the Catholic Medical Center of Queens and Brooklyn, New York.

Received for publication February 1, 1996.

Accepted for publication in revised form May 16, 1996.

DISCUSSION

The clinical picture could represent any of the disorders listed in the differential diagnosis. Bullous pemphigoid characteristically occurs in the sixth to eighth decade of life.¹ Large, tense bullae arise on clinically normal or erythematous skin, commonly on flexural surfaces of the forearms, the groin, the axillae, and the lower abdomen. Autoantibodies reactive with the basement membrane zone of skin and mucosae are present in serum samples from about 75% of the patients.² Histology reveals subepidermal bullae with sparse dermal perivascular eosinophilic infiltrates in non-erythematous skin.³ In inflamed skin, extensive accumulation of eosinophils intermingled with mononuclear cells and some neutrophils is seen,⁴ often to the extent of microabscesses of the tips of the papillae and sometimes cytotoxic vasculitis. Necrosis of keratinocytes may be seen in the epidermis. C'3, IgG, and other immunoglobulins are found in a linear pattern at the basement membrane zone. Response to systemic corticosteroids usually obviates use of immunosuppressive drugs.⁵ The patient's age and the distribution of the rash could represent bullous pemphigoid. The lack of eosinophils in the skin tissue renders this diagnosis less likely.

Erythema multiforme may develop in association with exposure to a variety of drugs and a host of infectious agents.⁶ Prodromal symptoms are uncommon. When present, they mimic an upper respiratory infection (cough, rhinitis, low-grade fever, and cervical lymphadenopathy). Typically, the rash develops abruptly with all the lesions appearing within three days. The variety of lesions runs from vesicular plaques to bullous lesions, with classic circular plaques which remain for several days, expand centrifugally and leave their centers cyanotic or purpuric—the iris, or target, lesion. Absence of symptoms is more common than pruritus. Healing lesions may leave local hyperpigmentation. The hallmark of the pathologic picture is

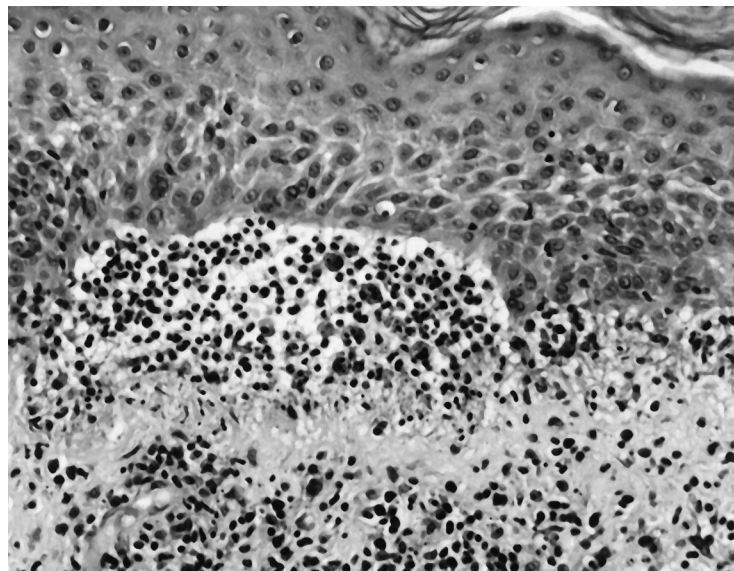


Figure 1. A peri-lesional skin specimen (original magnification $\times 400$). Infiltrates of neutrophils, plasma cells, and lymphocytes are present in the dermal papillae. The epidermis is intact.

exocytosis of dermal CD8⁺ lymphocytes into the epidermis,⁷ accompanied by necrosis of adjacent HLA-DR and intercellular adhesion molecule (ICAM)-1 positive keratinocytes,⁸ vacuolar degeneration of the basal layer and eventually separation of the necrotic epidermis and its basal membrane from the roof of the bullae. IgM, C'3, and fibrin deposits may be found in dermal blood vessels. Erythema multiforme usually runs a mild course and subsides spontaneously within 2 to 3 weeks. The lack of typical target lesions, the temporal relation to ciprofloxacin, which has only rarely been associated with erythema multiforme, and the microscopic findings of intact epidermis with leukocytoclastic vasculitis in the dermis do not fit the diagnosis of erythema multiforme.

Dermatitis herpetiformis has the characteristic finding of grouped, uniform, itchy vesicles with restricted distribution to the scalp, scapular area, extensor surfaces, and buttocks. The majority of the patients have gluten enteropathy, although many have no symptoms. These features were not present in our patient; however, the histologic picture of a dermal bulla with papillary “microabscesses” of

neutrophils in addition to a leukocytoclastic dermal vasculitis, virtually impels consideration of this diagnosis. Nevertheless, the lack of direct immunostaining with IgA is strong evidence against dermatitis herpetiformis, since a granular pattern of IgA staining of the dermal papillae is present in at least 90% of patients with this disorder.

Immunologic reactions to drugs may cause various eruptions identical in clinical appearance and in their histology to idiopathic cutaneous diseases. The histologic changes seen in skin lesions of fixed drug eruptions are most commonly epidermal.⁹ Bullae are formed by detachment of the epidermis from the underlying dermis.¹⁰ Lymphocytes, predominantly cytotoxic (CD8⁺), can be seen in the epidermis.¹ Immune complexes can be demonstrated in the walls of superficial dermal vessels. Basal epidermal cells may undergo hydropic degeneration, become dyskeratotic, and undergo phagocytosis by dermal macrophages containing large amounts of melanin.¹ That could be manifested as the residual dark discoloration of the affected skin subsequent to disappearance of the rash. Various other histologic pictures may be seen in drug eruptions,

including bullous systemic lupus erythematosus,¹² bullous pemphigoid, erythema multiforme, and even linear IgA disease.¹³

Our patient had a bullous rash with histologic features of dermatitis herpetiformis. This combination is not common in drug eruptions, and has not been reported with ciprofloxacin. According to the manufacturer (Miles, West Haven, CT—personal communication), urticaria developed during therapy at a rate of 50 cases per million; erythema multiforme, in only 10 cases to date; and dermatitis herpetiformis has never been reported. Analysis of data based on experience with 30,000 patients who received ciprofloxacin showed adverse reaction in the skin to be uncommon (1.4%), while gastrointestinal adverse reactions (5%) and elevated liver enzymes (4.5%) predominated.¹⁴ The dermatologic adverse effects that were documented included, (in order of frequency), rash, itching, and photosensitivity. Discontinuation of ciprofloxacin was not required in any patient. Another report, reviewing 9,400 treatment courses with ciprofloxacin, disclosed similar findings: cutaneous adverse effects were unusual (1.6%) and mild to moderate in severity.¹⁵ The reactions included rash in one-half the cases; pruritus in a third; and a few cases of hives, erythema, increased perspiration, and angioedema. In our institution ciprofloxacin was suspected in a case of toxic epidermal necrolysis (unpublished data).

Reports of generalized or severe skin disorders related to ciprofloxacin therapy are scarce. Erythema multiforme occurred in a woman with upper respiratory infection on the second day of ciprofloxacin therapy, concurrently with severe neutropenia.¹⁶ Concomitant drugs included cimetidine and misoprostol. Erythema multiforme was also reported in a patient with metastatic adenocarcinoma on the sixth day of ciprofloxacin, together with acute oliguric renal failure.¹⁷ In an elderly patient who received oral ciprofloxacin for a urinary tract infection, serum sickness developed on the second day

of therapy, and included generalized urticaria.¹⁸ This patient was also taking ibuprofen and phenazopyridine, both of which were reported to be associated with skin rashes.

The mechanism of adverse reaction to quinolones has not been established. Short of elucidating this mechanism, an attempt can be made to define the reported reactions according to the classification system of Patterson et al¹⁹ as modified by DeSwarte²⁰ and by Blass and deShazo²¹:

Classification of Adverse Drug Reactions.²²

Predictable

Overdose
Side effects
Secondary effects
Drug interactions

Unpredictable

Coincidental
Intolerance
Immunologic
Idiosyncratic

The first step is to characterize these events as predictable or unpredictable.

Predictable drug reactions include overdose (toxicity), side effects (common, undesired biologic responses to the medication), secondary effects (adverse outcomes of the biologic activity of the drug), and drug interactions.²² The skin reactions to ciprofloxacin cannot be considered predictable from the biologic (antibacterial) action of the drug. Overdose as a cause of these reactions is also unlikely: the safety profile of ciprofloxacin was comparable worldwide, despite differences of up to 40% in the doses used¹⁵; in the case reports of severe cutaneous reactions,^{16–18} usual doses of ciprofloxacin were used, and different concomitant drugs were taken in each case, with different indications. These facts also suggest that drug-drug or drug-disease interactions did not play a role.

Unpredictable drug reactions include intolerance (exaggerated adverse effects), idiosyncrasy (still unknown mechanism), and “allergic” (immune-mediated).²² Intolerance does not seem to explain the cutaneous reactions to ciprofloxacin, as dermatologic reactions generally have been uncommon and rarely severe.

Immunologic mechanisms appear to be more likely. These are usually classified according to the scheme of Gell and Coombs for hypersensitivity immune responses to antigens.²³ IgE-mediated reactions require presensitization to a molecule capable of acting as an antigen or a hapten. Two cases, in which “cross sensitivity” between quinolones was established, were reported: a fixed eruption subsequent to ciprofloxacin and to norfloxacin,²⁴ and a fixed eruption that was reproduced following separate oral challenges with each ciprofloxacin and ofloxacin.²⁵ These may suggest a molecular component common to these drugs, such as a complex of quinoline and piperazinyl residue, as an antigenic determinant. The occurrence, however, of skin reactions with the first exposure to ciprofloxacin in most of the cases reported is evidence against an IgE-mediated reaction. The inclusion of pruritus, urticaria, angioedema, and anaphylaxis among the skin reactions to ciprofloxacin may also suggest direct release of mast cell mediators via a complement-mediated anaphylactoid process, or by direct release of mediators by the drug. The reports of ciprofloxacin-related serum sickness and nephritis require consideration of reactions mediated by circulating immune complexes. The published reports did not mention measurement of such complexes, but in our patient a Raji cell assay was negative. Cellular-mediated hypersensitivity should also be considered, especially when the histologic picture typical of erythema multiforme is present. One case of a bullous rash following lomefloxacin documented the presence of activated helper-inducer memory T-lymphocytes (CD4⁺CD45RA⁺CD29⁺) in the blister fluid.²⁶ This subset of T cells has been shown to migrate selectively to delayed hypersensitivity lesions in human skin.²⁷ In summary, quinolone-induced cutaneous reactions appear to be mediated by immunologic processes, which may involve various mechanisms of hypersensitivity.

COURSE

The patient received hydrocortisone intravenously and gradually improved. She was able to leave the hospital on the eighth day of therapy, with tapering doses of corticosteroids. The rash has not recurred during 4 months of monitoring. In light of the history of hypersensitivity to penicillins, and the inability to complete a treatment course with ciprofloxacin and clarithromycin, the patient's future options of oral antibiotics were limited. Re-challenges with a quinolone or a macrolide could have been justified in attempt to identify the specific cause of the rash. The lack of involvement of mucous membranes and of vital organs, and the response to steroids could be used to predict a low risk from rechallenge. The patient, however, did not consent to a re-challenge with any medicine.

CONCLUSIONS

We present a case of a bullous rash that appeared during therapy with ciprofloxacin. The clinical presentation had some features of erythema multiforme, while the histologic picture was most consistent with dermatitis herpetiformis. Quinolones are uncommon causes of cutaneous reactions, and bullous dermatoses are even rarer. The clinical-pathologic combination in our patient was especially exceptional, as dermatitis herpetiformis-like processes are not usually seen in drug eruptions. The entire clinical course, including the original upper respiratory symptoms, could have reflected primary erythema multiforme. Nevertheless, the possibility of a drug-induced process that kept progressing despite discontinuation of the drug, and the atypical histologic picture, led us to intervene with large doses corticosteroids. Although a re-challenge with the drug was not feasible, we believe that the temporal association implicates ciprofloxacin. Bullous rashes in temporal association with medications should always be suspected, among other possibilities, as drug-eruptions, even when

the medication is considered an unlikely offender.

REFERENCES

1. Jordon RE. The immunobullous diseases. In: Lebowitz M, ed. *Difficult diagnoses in dermatology*. New York: Churchill Livingstone, 1980:113–31.
2. Jordon RE, Canawa S, Fritz KA. Immunopathologic mechanisms in pemphigus and bullous pemphigoid. *J Invest Dermatol* 1985;85:725–31.
3. Eng AM, Moncada B. Bullous pemphigoid and dermatitis herpetiformis. Histologic differentiation. *Arch Dermatol* 1978;110:51–7.
4. Jablonska S, Chorzelski TP, Beutner EH, et al. Dermatitis herpetiformis and bullous pemphigoid: intermediate and mixed forms. *Arch Dermatol* 1976;112:45–8.
5. Millikan LE. Vesiculobullous skin disease with prominent immunologic features. *JAMA* 1987;258:2910–5.
6. Fritsch PO, Elias PM. Erythema multiforme and toxic epidermal necrolysis. In: Fitzpatrick TB, Eisen AZ, Wohl K, Freedberg IM, Austen KF, eds. *Dermatology in general medicine*. New York: McGraw-Hill, 1993:585–96.
7. Margolis RS. Lymphocytes subsets and Langerhans cells/indeterminate cells in erythema multiforme. *J Invest Dermatol* 1983;81:403–7.
8. Nickolof. The role of adhesion molecules, chemotactic factors and cytokines in inflammatory and neoplastic skin disease—1990 update. *J Invest Dermatol* 1990;94:151s–60s.
9. Non-infectious vesicular and bullous diseases. In: Lever WF, Schaumburg-Lever, eds. *Histopathology of the skin*. Philadelphia: Lippincott, 1990:103–51.
10. Korkij W, Soltani K. Fixed drug eruption. A brief review. *Arch Dermatol* 1984;120:520–4.
11. Masu S, Seiji M. Pigmentary incontinence in fixed drug eruptions. *J Am Acad Dermatol* 1983;8:525–32.
12. Landor M, Rosenstreich DL. Vesiculobullous rash in a patient with systemic lupus erythematosus. *Ann Allergy* 1993;70:196–203.
13. Argenyi ZB, Bergfeld WF, Valenzuela R, et al. Adult linear IgA disease associated with an erythema multiforme-like drug reaction. *Cleveland Clin J Med* 1987;54:445–50.
14. Halkin H. Adverse effects of fluoroquinolones. *Rev Infect Dis* 1988;10(suppl 1):s258–61.
15. Schacht P, Arcieri G, Hullman R. Safety of oral ciprofloxacin. *Am J Med* 1989;87(suppl 5A):98–102s.
16. Imrie K, Gold W, Salit I, Keating A. Ciprofloxacin-induced neutropenia and erythema multiforme. *Am J Hematol* 1993;43:159–60.
17. Allon M, Lopes E, Kyung-Whan M. Acute renal failure due to ciprofloxacin. *Arch Intern Med* 1990;150:2187–9.
18. Guharoy S. Serum sickness secondary to ciprofloxacin use. *Vet Human Toxicol* 1994;36:540.
19. Patterson R, DeSwarte RD, Greenberger PA et al. Drug allergy and protocols for management of drug allergies. *Allergy Proc* 1994;15:289–64.
20. DeSwarte RD. Drug allergy: an overview. *Clin Rev Allergy* 1986;4:443–69.
21. Blass MS, deShazo RD. Drug allergy. *Pediatr Clin N Am* 1988;35:1131–47.
22. Rieder M. Mechanisms of unpredictable adverse drug reactions. *Drug Safety* 1994;11:196–212.
23. Coombs RRA, Gell PGH. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Coombs RRA, Gell PGH, eds. *Clinical aspects of immunology*. New York: FA Davis, 1968:575–96.
24. Alonso M, Martin J, Quirce S, et al. Fixed eruption caused by ciprofloxacin with cross sensitivity to norfloxacin. *Allergy* 1993;48:296–7.
25. Kawada A, Hiruma M, Morimoto K, et al. Fixed drug eruption induced by ciprofloxacin followed by ofloxacin. *Contact Dermatitis* 1994;31:182–3.
26. Correia O, Delgado L. Bullous photo-dermatitis after lomefloxacin. *Arch Dermatol* 1994;130:808–9.
27. Pitzalis C, Kingsley GH, Covelli M, et al. Selective migration of the human helper-inducer memory T cell subset: confirmation by in vivo cellular kinetic studies. *Eur J Immunol* 1991;21:369–76.

Request for reprints should be addressed to:
Michael Landor, MD
Department of Medicine
St. John Hospital
90-02 Queens Boulevard
Elmhurst, NY 11373