Accelerated cell-mediated immune reactions in penicillin allergy

Richard J. Warrington, MD,[a] Fanny Silviu-Dan, MD,[a] and Cynthia Magro, MD[b] *Winnipeg, Manitoba, Canada*

The causes of maculopapular eruptions in penicillin allergy are ill defined. They may be cell-mediated in origin, because sometimes lymphocyte proliferative responses can be induced with the implicated drug in vitro and there are occasional reports of delayed-onset skin-test reactions in patients who are tested for penicillin allergy.[1, 2]

This investigation was precipitated by the finding in two patients with maculopapular rashes induced by ampicillin and piperacillin, respectively, of a delayed-onset specific reaction to skin testing with the appropriate semisynthetic penicillin skin test reagent, in the absence of an immediate hypersensitivity response.

CASE REPORTS

Patient 1

A 42-year-old woman received ampicillin for treatment of a urinary tract infection. After 1 day of treatment, a pruritic generalized maculopapular rash, sparing the face, developed. There was no angioedema or other associated symptoms. The ampicillin was stopped, and the rash resolved within a few days.

Patient 2

A 57-year-old woman with acute myeloid leukemia in remission received piperacillin and gentamicin for treatment of a fever, and within 1 day a generalized pruritic maculopapular rash, with subsequent palmar desquamation, developed. The piperacillin was stopped, and the rash resolved within 4 days. There were no other associated symptoms.

METHODS

Skin Testing

Skin testing was carried out within 4 weeks of the initial reaction in patient 1 and was repeated 2 months later. In patient 2, skin testing was performed within a few days of the reaction and again 6 months after the reaction. The test results were the same on both occasions.

Abbreviation used
MDM: Minor determinant mixture

The testing was carried out with a major determinant preparation of benzylpenicilloyl poly-L-lysine (6×10^{-5} mol/L; Kremers-Urban, Milwaukee, Wis.) and with minor determinant mixtures (MDMs) benzylpenicillin MDM, ampicillin MDM, amoxicillin MDM, or piperacillin MDM, all at 2×10^{-2} mol/L, prepared by the method of Levine et al. (1966).[3] Prick testing was done first, followed by intradermal testing if results of the prick test were negative. Histamine was used as a positive control, with saline as the negative control.

Skin biopsy

A punch biopsy was taken from patient 2, with the patient's consent, 26 hours after intradermal testing, at the site of the positive skin test reaction to piperacillin MDM. A portion of this biopsy specimen was fixed and stained for light microscopy. Frozen sections of an unfixed portion of the specimen were stained respectively for IgG, IgA, IgM, C1q, C3, and fibrin by immunofluorescence. Additional frozen sections were analyzed for expression of CD3 (anti-Leu-4), CD4 (anti-Leu-3), CD8 (anti-Leu-2), CD19 (anti-Leu-12), and HLA-DR (Becton Dickinson, Mountain View, Calif.) by immunoperoxidase staining. It was not possible to retest and perform a biopsy patient 1.

RESULTS

In both patients and on both occasions, results of all prick tests except for the histamine positive control were negative. Intradermal skin test results in both cases were negative to all test reagents at 12 minutes. Within about 9 hours, reactions began at the ampicillin MDM and amoxicillin MDM intradermal test sites in patient 1 and at the piperacillin MDM test site in patient 2. By 24 hours, large erythematous indurated reactions were present at the test sites of ampicillin MDM (8×18 mm) and amoxicillin MDM (8×10 mm) in patient 1 and with piperacillin MDM (8×10 mm) in patient 2. In both cases, reactions faded by 72 hours.

From the Departments of [a]Medicine and [b]Pathology, University of Manitoba, Winnipeg, Manitoba, Canada.
J ALLERGY CLIN IMMUNOL 1993;92:626-8.

0091-6749/93 $1.00 + .10 **1/54/48467**

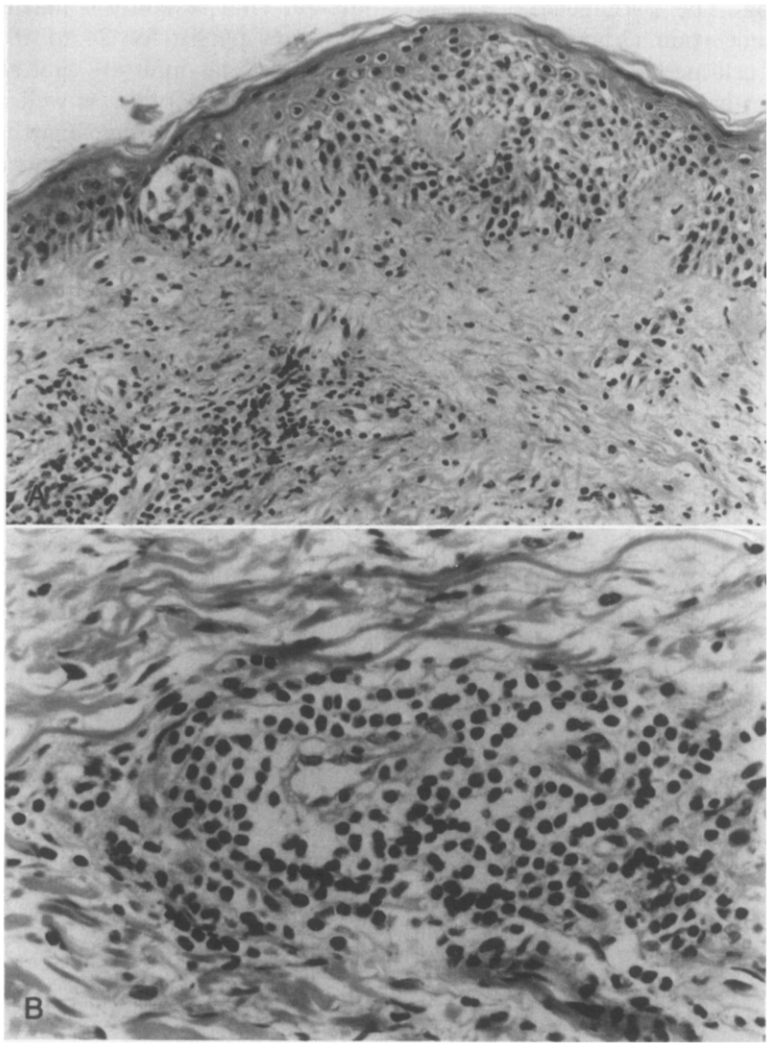

FIG. 1. The skin biopsy specimen shows a perivascular lymphocytic infiltrate associated with epidermal spongiosis and formation of microvesicles: **A,** magnification ×20; **B,** magnification ×40. Virtually all of the cells within the infiltrate are T cells strongly reacting with Leu 4. There is a mixture of CD4 and CD8 cells with a predominance of CD4.

The biopsy specimen from patient 2 revealed a striking epidermal and dermal inflammatory reaction. There were dense activated lymphoid infiltrates that surrounded and permeated the postcapillary venules, with evidence of vascular injury (Fig. 1, *A* and *B*). This latter phenomenon was manifested by endothelial swelling and necrosis, fibrin deposition, and mural edema. The epidermal changes were those of a vasculopathic lymphocyte-rich interface dermatitis with an additional component of acute eczematous changes manifested by lymphocyte and Langerhans cells containing microvesicles and spongiosis. The biopsy findings were consistent with a severe delayed hypersensitivity reaction.

Immunofluorescence studies showed only deposition of small amounts of IgM with traces of C1q, C3, and fibrin. Immunoperoxidase staining demonstrated that the infiltrate was predominated by CD3-positive cells, of which the majority expressed CD4 with a minor population that was CD8-positive. No B cells were present. The vascular endothelium was strongly HLA-DR–positive.

DISCUSSION

Maculopapular or morbilliform eruptions are seen quite commonly in patients who are receiving penicillins, particularly the semisynthetic penicillins. Usually these reactions occur after 4 days

or more of therapy. The pathogenetic mechanisms involved are uncertain, although sometimes there is evidence of cell-mediated immunity to the penicillins in vitro or in vivo.[1, 2]

The patients described here had maculopapular rashes within 1 day of receiving the semisynthetic penicillins, ampicillin and piperacillin, respectively. When skin testing with benzylpenicillin and semisynthetic penicillin skin test reagents was done, there was a delayed reaction at the intradermal skin test sites to the implicated semisynthetic penicillin reagents or the closely related derivative, that is, to ampicillin and amoxicillin or to piperacillin but no reaction to the major and minor determinants of benzylpenicillin. The reactions began at 9 to 12 hours and were maximal at 24 hours, fading by 72 hours, which mimicked the clinical course of the reactions.

Immunofluorescence showed no evidence for an antibody-mediated reaction. There was a marked lymphocyte reaction, and the distribution of the infiltrate and concomitant epidermal changes were characteristic of a marked delayed-type hypersensitivity response, with the predominant infiltrate being T cells expressing the CD4 antigen. There was a minor CD-8 positive component, and there were no B cells. The vascular endothelium itself strongly expressed HLA-DR antigen.

The reaction reported here is quite different from the cutaneous late-phase response, which typically follows an immediate hypersensitivity reaction. That response is maximal at 4 to 8 hours and may persist for 24 to 48 hours. There is a mixed cellular infiltrate that contains both eosinophils and basophils, as well as some CD4-positive T cells. Neutrophils may be present early and late in the reaction.[4] In contrast, the typical cell-mediated immune response in the skin consists of a mononuclear cell infiltrate with CD4-positive and CD8-positive T cells, which peaks at 24 to 48 hours and lacks a significant contribution from polymorphonuclear leukocytes.

There is therefore clinical and skin test evidence of a rapid cell-mediated immune response apparently specific for side-chain determinants in these two cases of maculopapular rash induced by semisynthetic penicillins. It is unclear how T cells recognize the small antigenic determinants expressed on the side chains of such molecules as ampicillin, amoxicillin, or piperacillin and distinguish them from benzylpenicillin.

We thank Dr. Eric Bow for allowing us to study his patient and Heather Gray for typing the manuscript.

REFERENCES

1. Ahlstedt S, Kristofferson A. Immune mechanisms for induction of penicillin allergy. Prog Allergy 1982;30:67-134.
2. Vega JM, Blanca M, Carmona MJ, et al. Delayed allergic reactions to beta lactams. Allergy 1991;46:154-7.
3. Levine BB, Redmond AP, Fellner MJ, et al. Penicillin allergy and the heterogenous immune responses of man to benzylpenicillin. J Clin Invest 1966;45:1895-1906.
4. Lemanske RF Jr. The late phase response: clinical implications. Adv Intern Med 1991;36:171-93.

Bird-egg syndrome in childhood

Belén Añíbarro, MD, M. Carmen García-Ara, MD, and J. Antonio Ojeda, MD *Madrid, Spain*

In 1985 Maat-Bleeker et al.[1] described the first case of allergy to egg yolk possibly induced by respiratory sensitization to bird serum antigens. This peculiar sensitization has been designated as "bird-egg syndrome."[2] To date, no case has been described in children. We report a child with exposure to birds who experienced asthma caused by bird feathers when he was 5 years old and food allergy to egg 1 year later.

From the Allergology Service, La Paz Hospital, Madrid, Spain.
Reprint requests: B. Añíbarro, MD, Fermín Caballero 90, 8B, Madrid 28035, Spain.
J ALLERGY CLIN IMMUNOL 1993;92:628-30.

0091-6749/93 $1.00 + .10 **1/54/48470**

CASE REPORT

An 8-year-old boy with a family history of atopy had perennial asthma for the last 3 years. He had goldfinches and canaries at home, and the symptoms improved partially when the birds were removed. He reported immediate asthma when he was in contact with hens.

He had never experienced any symptoms of food allergy until 2 years ago when he refused to eat eggs because he said it resulted in cough, abdominal pain, vomiting, and throat pruritus. However, he showed no reaction to chicken meat.

Results of physical examination were unremarkable. The complete blood count and chemistry were normal except for eosinophilia (1000 cells/ml). Chest roentgenogram and results of spirometry were normal. A methacholine test revealed bronchial hyperreactivity.