

Drug reaction to ceftriaxone in a child with X-linked agammaglobulinemia

To the Editor:

We report the case of a drug reaction occurring in a child with X-linked agammaglobulinemia (XLA) in the absence of IgE and demonstrate the involvement of T cells in the pathogenesis.

The patient was a 5-year-old white boy with XLA on monthly infusions of intravenous gammaglobulin and prophylactic trimethoprim/sulfamethoxazole (Bactrim, Roche Labs, Nutley, NJ) since birth. He sustained a hand infection that was treated initially with amoxicillin/clavulanate potassium (Augmentin, Smith Kline Beecham, Collegeville, Pa) for 10 days and then by incision and drainage. The wound culture grew β -lactamase-positive, coagulase-negative *Hemophilus influenzae*, so he was treated with intravenous infusions of ceftriaxone 2 g/d (Rocephin, Roche Labs, Nutley, NJ), an antibiotic to which he had no prior exposure. After the sixth dose of ceftriaxone, he developed a diffuse, maculopapular rash with minimal pruritus, hyperthermia, flushing, and lethargy. Because of his diagnosis, an IgE mechanism was not suspected; therefore, the seventh dose of ceftriaxone was given the following day, after the rash had improved and the hyperthermia resolved. Within minutes, he had a recurrence of the rash with severe itching, flushing, and hyperthermia. The infusion was immediately stopped and the reaction was treated with histamine receptors 1 and 2 blockers and oral steroids for 36 hours until resolution of symptoms.

The patient's brother with XLA had a 2.6-kb deletion involving exons 8, 9, and 10 of the Bruton's tyrosine kinase gene with exon 7 spliced directly to 11 (unpublished communication, Mary Ellen Conley, MD, St Jude's Children's Research Hospital, Memphis, Tenn.).

At 6 days of age, the patient's lymphocytes, immunophenotyped by flow cytometric analysis, had been as follows: CD3⁺, 6274 (2280-6450); CD4⁺, 4755 (1690-4600); CD8⁺, 1651 (720-2490); CD19⁺, <66 (600-3000), and CD16⁺, 198 (100-1300) cells/mm³. Immunoglobulin levels as determined by nephelometry were as follows: IgG, 861 (240-900); IgA, <0.9 (130-520), and IgM, 4 (190-830) mg/L. At 10 months, in vitro T-cell proliferation to phytohemagglutinin A, concavalin A, and pokeweed mitogen, measured by H³-Thymidine incorporation, was normal. At the time of the drug reaction, serum IgE was 0.6 U/mL (<30).

Four weeks after the resolution of the drug reaction, skin tests were done to assure that his reaction was not IgE-mediated, because rare cases of XLA have presented low levels of serum IgE.^{1,2} Results of skin prick testing on the volar surface of the forearm with Pre-pen (6 × 10⁻³ mol/L benzylpenicilloyl, Schwarz Pharma, Inc, Milwaukee, Wis), penicillin (6000 units/mL), ceftriaxone (3 mg/mL), and saline solution and intradermal testing with 0.1 mL of Pre-pen, penicillin (6000 units/mL), and ceftriaxone (0.03 mg/mL) were negative with a positive histamine (1 mg/mL) reaction.

Drug patches, made by diluting the drug ceftriaxone to 30% w/v in both petrolatum and saline solution,³ and controls were applied to the upper back of the patient with Finn chambers on Scanpor tape (Epitest, Tuusula, Finland) and read after 48 hours. An area of induration 10 mm in diameter developed at the ceftriaxone site but not at the control site. A 4-mm skin punch biopsy specimen was obtained from the positive patch test site after cleaning and administration of local anesthesia with 2% lidocaine. After formalin fixation, sections of the paraffin block were cut at 5 μ m and stained with hematoxylin and eosin (Fig 1, A) and with antibodies to CD4 (Novocastra, Newcastle upon Tyne, United Kingdom) 1:20 dilution, CD7 (Novocastra) 1:75 dilution, CD8 (Dako, Carpinteria, Calif) 1:20 dilution after antigen retrieval (Fig 1, B), and CD45RO

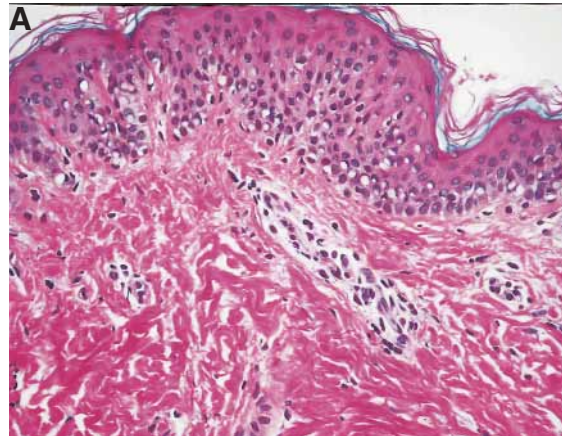


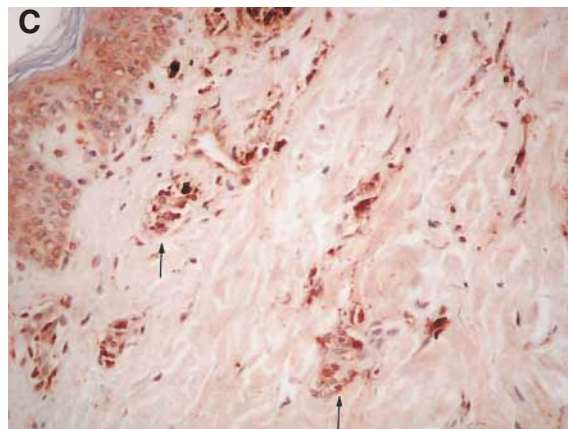
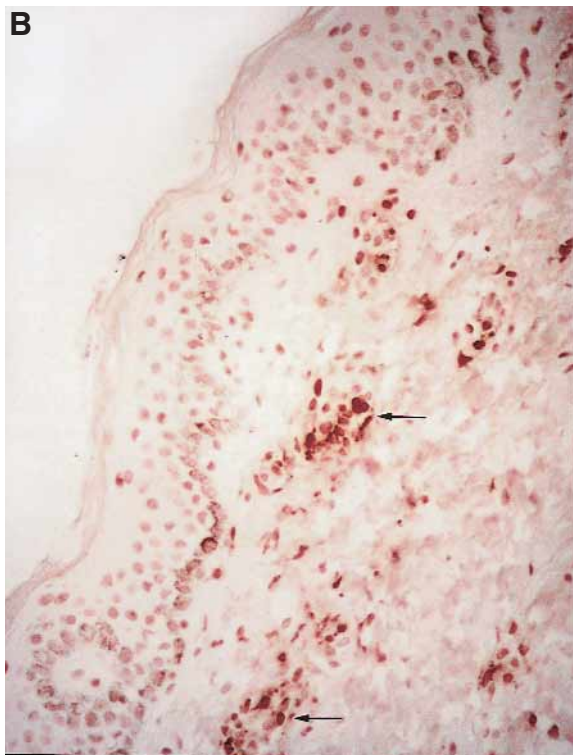
FIG 1. Punch biopsy of the positive patch test site. **A**, Hematoxylin and eosin staining shows spongiosis of the epidermis with basal layer vacuolization. There is a scant perivascular mononuclear cell infiltrate in the upper dermis. (Figure continued on next page.)

(UCHL-1; Dako) 1:200 dilution after trypsin digestion (Fig 1, C). The perivascular mononuclear cell infiltrate in the upper dermis stained positive for CD4, CD7, and CD45RO.

In vitro CD4⁺ T-cell proliferation to ceftriaxone was done by IBT Laboratories (Lenexa, Kan) by measuring adenosine triphosphate (quantified through use of a luciferin-luciferase system [Sigma Chemicals] and a Berthold luminometer [Lumat LB9501]) produced during activation of the CD4⁺ cells from the patient's blood cocultured overnight with ceftriaxone 0.5 mg/mL and 5.0 mg/mL diluted in RPMI. Unstimulated blood from the patient was used as a negative control.⁴ There was no T-cell proliferation to ceftriaxone, whereas there was normal proliferative response to mitogens.

The role of T cells in adverse drug reactions is controversial because T cells recognize peptide antigens and not the low-molecular-weight compounds of which drugs are an example. Recently, drug-specific CD4⁺ and CD8⁺ T cells in the skin and the peripheral blood of patients with maculopapular drug eruptions have been identified through use of immunohistochemistry analysis. In addition, coculture with β -lactam antibiotics or their metabolites stimulated peripheral blood mononuclear cells from subjects with hypersensitivity reactions.⁵ When the T cells are stimulated by exposure to the drug, a variety of cytokines can be produced, leading to clinical manifestations. Cytokines produced by T_H2 cells were shown to play an important role in β -lactam-induced allergic reactions, even when an IgE-mediated mechanism is apparently not demonstrable.⁶ Alternatively, T_H1-like CD8⁺ dermal T cells were shown to be primarily involved in delayed cutaneous adverse reactions.⁵

Our patient with XLA had absent B cells, no demonstrable serum IgE or penicillin, and ceftriaxone-specific IgE, though a negative skin test to cephalosporins does not have a definite predictive value. The initial reaction was difficult to differentiate from an IgE-mediated reaction, but the clinical course was indicative of an adverse drug reaction, inasmuch as an additional dose resulted in exacerbation of the cutaneous symptoms. Because T cells have been implicated in such adverse drug reactions, in vivo evidence of T-cell



B, Perivascular cells stained with antibody to CD45RO and appear dark (arrows). **C**, Perivascular cells stained with anti-CD4 and appear dark (arrows). Most perivascular mononuclear cells also stained with anti-CD7 but not with anti-CD8.

involvement was sought. The T-cell studies were done 1 year after the clinical reaction; therefore, the lack of a recent exposure to the drug might explain the absence of an *in vitro* proliferative response of the circulating T cells to ceftriaxone. However, the positive patch test and skin biopsy results indicate that the drug-reactive T cells have homed to the skin—hence the cutaneous nature of the reaction. The antibody staining of the skin at the positive patch biopsy site demonstrated that the T cells present are of the T helper subset and are predominantly of the memory T-cell phenotype, with positive staining to CD45RO.

This case offers the first definite evidence that adverse drug reactions manifested as morbilliform or maculopapular rashes occur in the absence of IgE and that CD4⁺ T cells are effector cells in the reaction.

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1/8/123536

doi:10.1067/mai.2002.123536