

# Azithromycin Eruption in Infectious Mononucleosis: A Proposed Mechanism of Interaction

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*The penicillin family of antibiotics may induce drug eruptions when prescribed to patients with infectious mononucleosis. Very similar phenomena have also been cited with other antibiotic families. We report the first case of a cutaneous reaction in a patient with infectious mononucleosis treated with azithromycin. We propose an immune-based hypothesis to explain the transient sensitivity resulting in this secondary cutaneous eruption.*

Cutaneous eruptions associated with antibiotic use and infectious mononucleosis (IM) are common and well documented. This phenomenon has been observed with ampicillin, amoxicillin, methicillin, and the ampicillin derivatives of pivampicillin and talampicillin.<sup>1,3</sup> A very similar, yet distinct eruption has been described with erythromycin use in patients infected with the Epstein-Barr virus (EBV).<sup>4</sup> More recently, a drug eruption associated with IM has been documented with cephalexin treatment.<sup>5</sup> The following report illustrates the first case of a young man with IM who exhibited a generalized cutaneous eruption following treatment with azithromycin.

## Case Report

A 20-year-old white man presented to the dermatology clinic for evaluation of a mildly pruritic, disseminated cutaneous eruption of erythematous macules, papules, and patches. He was well until 2 weeks be-



**FIGURE 1.** Anterior view of the generalized eruption of erythematous macules, papules, and patches.

fore presentation when he noted the development of upper respiratory infection (URI) symptoms, generalized malaise, and tender joints. He was empirically treated with a 5-day course of azithromycin for a suspected streptococcal throat infection without resolution of his symptoms. The follow-up physical examination 7 days later revealed persistence of the

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REPRINTS are not available.



**FIGURE 2.** Posterior view of the generalized eruption of erythematous macules, papules, and patches.

superficial, minimally tender, cervical lymphadenopathy. The pharynx was clear except for some mild persistent posterior erythema. A centrally located maculopapular eruption was noted on the trunk, and the patient was referred to dermatology after a mono-spot, complete blood count (CBC), liver function tests (LFT), and chemistry analyses were ordered.

The following morning, the patient presented to the dermatology clinic with an extensive cutaneous eruption on the trunk and extremities with confluent patches centrally and mild pruritus. Review of systems was noncontributory except for the URI symptoms. His medications included azithromycin and acetaminophen (Tylenol®).

Physical examination revealed a well-developed, well-nourished, afebrile young man with diffuse, symmetric, erythematous, nontender macules, papules, and confluent patches. These areas of blanchable erythema extended from the neck to the ankles (Figures 1 and 2). The palms and soles were spared. There was no oral involvement, except for the mild posterior pharyngeal erythema, nor involvement of the genital or anal mucosa. His lungs were clear to auscultation and there was no hepatosplenomegaly.

Laboratory findings included a positive mono-spot, white blood cell count of 11.7 with a differential of 27% mononuclear cells and 68% lymphocytes. The hemoglobin, hematocrit, urinalysis, and LFTs were within normal limits and a throat culture was negative. These findings were consistent with a diagnosis of IM.

Due to the temporal relationship of the azithromycin administration and the cutaneous changes, the diagnosis of an azithromycin rash associated with IM was made. The patient was treated with topical 0.1% triamcinolone cream applied twice daily and 25 mg of oral hydroxyzine every 4 to 6 hours. The pruritus rapidly improved over the following 2 days. The cutaneous eruption resolved over the following 5 weeks.

### Comments

Before the development of the mono-spot diagnostic test, the incidence of a primary cutaneous eruption associated with EBV-induced IM was high and considered commonplace.<sup>6,7</sup> Once the physician was able to quickly confirm the diagnosis of IM with the mono-spot test, fewer primary associated skin eruptions were reported.<sup>1,3</sup> The morphology of a primary IM-associated cutaneous eruption is nonspecific, maculopapular, scarlatiniform or erythema multiforme-like, and similar to many other viral eruptions. There is no specific diagnostic test to confirm that the cutaneous lesions represent a primary viral exanthem.<sup>1,5</sup>

We propose that many of the previously noted cutaneous eruptions of IM were actually antibiotic eruptions in the setting of an altered immune state resulting from the EBV infection. Without the aid of a rapid diagnostic test (mono-spot), ampicillin or another member of the penicillin family was frequently prescribed for patients with upper respiratory symptoms of fever, sore throat, cough, and malaise. In most cases, the underlying infectious cause was not EBV and the symptoms would resolve without a cutaneous reaction. In those cases associated with an EBV infection, a virally induced immune response might result in a "secondary" cutaneous drug eruption.

Cutaneous eruptions with the use of ampicillin in the absence of EBV infection have an incidence of less than 5:100.<sup>8-10</sup> Two distinct cutaneous presentations are described. The first is urticarial in nature, and appears to be a type I Gell-Coombs reaction, mediated through an IgE immediate type hypersensitivity, as seen with a true penicillin allergy. The second type is a non-IgE, delayed type hypersensitivity (Gell-Coombs type IV) cutaneous eruption. This delayed type hypersensitivity reaction has been reported as an erythematous maculopapular reaction. This type of presentation may or may not be associated with fever.<sup>10-12</sup>

A morbilliform eruption has also been described with an increased incidence in patients treated with ampicillin who have a concomitant EBV infection.<sup>1-5</sup> This type of drug reaction may be associated with the immunologic abnormalities observed in patients with IM. Patients infected with EBV have an excess of abnormal circulating lymphocytes.<sup>1,3,13</sup> This excess is manifested as an absolute increase in T lymphocytes.<sup>13</sup> If the increased numbers of T lymphocytes in a patient infected with EBV are activated to differentiate along the Th-1 lineage, they will produce predominantly interleukin (IL)-2, interferon (IFN)-gamma, and tumor necrosis factor-alpha cytokines. These cytokines orchestrate cell-mediated immunity. Interleukin-2 promotes further growth and stimulation of the T lymphocyte. Interferon-gamma and tumor necrosis factor-alpha have proinflammatory properties, one of which is fever. Interferon-gamma inhibits Th-2 type T lymphocytes, and down-regulates IL-4 required for the growth and development of B lymphocytes, which are Th-2 cytokine dependent. The other cytokines produced by Th-2 lymphocytes are IL-5, IL-6, and IL-10.<sup>14,15</sup>

Interleukin-10 suppression of Th-1 lymphocytes is an extremely interesting concept in this setting, for tolerance may be lost if IL-10 is not present. Tolerance is a specific loss of immunologic responsiveness. Loss of tolerance may result in hypersensitivity to an antigen encountered at that time.<sup>14,15</sup> That antigen in this case may be the readily available polymerization of ampicillin in solution. This is supported by Webster and Thompson,<sup>16</sup> who cultured peripheral blood leukocytes with an ampicillin polymer and found that these leukocytes incorporated radioactively labeled thymidine faster than those that were not stimulated by addition of the ampicillin polymer. Therefore, if one already has an increased population of activated Th-1 cells in patients with an acute EBV infection leading to low IL-10 levels, and then is further stimulated by high molecular-weight-soluble antigens of penicillin, erythromycin, cephalosporins, or in this case azithromycin, this may result in a hyper-reactive state from the loss of IL-10-mediated tolerance. This could result in a transient Th-1 lymphocyte-mediated delayed type hypersensitivity reaction to the medication, expressed clinically as a drug eruption.

This is supported by Lund and Bergan,<sup>17</sup> who noted a temporary increase in intradermal skin reactions to penicillin during the acute stage of IM. During the acute stage (defined as: a positive mono-spot or heterophilic antibody titer > 40; white blood cell count > 4500/mm<sup>2</sup> with a > 50% lymphocyte shift; and clinical manifestations of IM), 84% of their patients had a positive cutaneous reaction to penicillin expressed clinically as a morbilliform drug eruption.<sup>17</sup>

A comparable immunologic setting may be present in patients suffering from lymphatic leukemia. These patients have an increased incidence of ampicillin-related cutaneous eruptions similar to those observed in patients infected with EBV.<sup>18</sup> This may also be due to an increased population of abnormal, yet immunologically competent, lymphocytes resulting in a delayed type hypersensitivity reaction to medication, expressed clinically as a drug eruption. This transient, or virally induced, population of immunologically hyper-reactive Th-1 lymphocytes may explain the temporary nature of the cutaneous reaction to ampicillin in patients infected with EBV. Nazareth *et al.*<sup>19</sup> have shown that ampicillin may be safely prescribed to patients who have had a previous cutaneous reaction to ampicillin during an episode of IM. Once the acute viral infections resolve, these individuals would no longer maintain an increased population of abnormal Th-1 lymphocytes, thus the down-regulation of Th-2 lymphocytes would be lost. The patient could then mount a regulatory IL-10 response resulting in tolerance to the antigen.

The most intriguing support comes from a mechanism that the EBV itself employs for evading the immune system through its own cytokine manipulation. Epstein-Barr virus encodes a gene product, BCRF1, that has more than 80% homology with human IL-10, during the late phase of the viral cycle.<sup>18,19</sup> During the acute EBV infection, however, only a limited number of viral genes are expressed.<sup>20</sup> This may allow a brief period of Th-1 cytokines to prevail, resulting in the cutaneous reaction. Tolerance to the antigens would then be established as the latent viral genome of the EBV increases the BCRF1/IL-10-like gene product. This BCRF1 response may be the virus's attempt to impair the immune system's ability to eliminate the virus. If the virus can avoid inducing a Th-1-dominated response, it will evade the antiviral effects of IFN-gamma as well.

Cutaneous eruptions associated with antibiotic use in patients infected with the EBV are well established. The most common antibiotics cited are the penicillins, but eruptions have also been noted with erythromycin and cephalexin. The interaction between the altered immune state and the antibiotic exposure that results in a cutaneous eruption is not clearly understood. Our proposed hypothesis of a transient increased population of abnormal Th-1 lymphocytes may explain the susceptibility for the drug eruption, but investigations to evaluate our hypothesis are needed. This is the first report of such an eruption with azithromycin treatment in a patient with EBV, and we do not wish to condemn the use of antibiotics in clinically indicated settings. There may be no "safe" antibiotic to prescribe in the setting of IM. Our purpose here is simply to heighten physician awareness of the interaction of all antibiotics

and IM and possibly raise the “Barr” of understanding to a higher level.

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