
Case report

Intrapartum anaphylaxis to penicillin in a woman with rheumatoid arthritis who had no prior penicillin allergy

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Background: Little is known about the development of drug allergy during pregnancy or in patients with altered immune status.

Objective: To report a case of new-onset penicillin allergy during pregnancy in a woman with rheumatoid arthritis.

Methods: A 39-year-old woman with rheumatoid arthritis developed intrapartum anaphylaxis that led to fetal demise. She had previously received penicillin-based antibiotics without any allergic reactions. Because of group B streptococcus colonization, an intravenous infusion of penicillin G was started during labor. Within minutes, she developed severe anaphylaxis.

Results: A fluorescent enzyme immunoassay revealed a moderate level of specific IgE to penicilloyl G and penicilloyl V (3.15 kU/L and 2.77 kU/L, respectively). Given the patient's history, these positive results were considered confirmatory of penicillin allergy. This case raises a number of salient points. First, patients can develop severe allergy to penicillin despite having safely received penicillins in the past. Possible factors that influenced the development of severe penicillin sensitivity in this patient are discussed. Second, unexpected intrapartum anaphylaxis can occur, which can be life threatening to the mother or fetus. Third, safe and reliable methods for diagnosis of drug allergy must be available.

Conclusions: This case illustrates that during the current unavailability of skin testing reagents in the United States, a positive result on in vitro testing can be helpful in confirming penicillin allergy in cases in which drug challenge is deemed unsafe.

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INTRODUCTION

We have learned a great deal about drug hypersensitivity during recent decades, but much still needs to be learned. In the United States, approximately 10% of individuals report “penicillin allergy” by history, but studies have shown that the prevalence of true IgE-mediated allergy is approximately 1%.^{1–4} The development, as well as the first manifestation, of penicillin allergy can occur at any age. However, little is known about the development of drug allergy during pregnancy or in patients with altered immune status such as autoimmune disease. Reported herein is a case of new-onset penicillin allergy during pregnancy in a woman with rheumatoid arthritis (RA).

REPORT OF CASE

A 39-year-old woman was referred for evaluation after intrapartum anaphylaxis. She had previously received penicillin and other penicillin-based antibiotics without any allergic reactions. In fact, she had received a course of oral amoxi-

cillin during the first trimester of her pregnancy. Because of group B streptococcus colonization, an intravenous infusion of penicillin G had been started during labor. Within a minute, she developed dyspnea and malaise, with rapid progression to profound hypotension. Epinephrine was administered, and an emergency cesarean section was performed. The patient recovered postoperatively; however, the infant died of asphyxia.

The patient's medical history was remarkable for hypothyroidism and RA, and she had been treated with levothyroxine, methotrexate, hydroxychloroquine, etanercept (Enbrel), and adalimumab (Humira) at varying times. However, levothyroxine was her only regular medication during pregnancy.

Timing of the anaphylactic reaction suggested that it was due to penicillin G, but other drugs had also been administered during the intrapartum period. Therefore, confirmation that penicillin was the agent to which the patient was allergic was important. Challenge with penicillin was deemed unsafe because of the severity of the reaction. Because of the lack of commercial availability of appropriate skin testing reagents, penicillin specific IgE was evaluated using the Pharmacia ImmunoCAP radioallergosorbent test fluorescent enzyme immunoassay, which revealed a moderate level of specific IgE to penicilloyl G and penicilloyl V but no significant specific IgE to intact ampicillin and amoxicillin antigens (Table 1).

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Table 1. Pertinent Laboratory Results

Test	Result, kU/L	Reference range, kU/L
Penicilloyl G IgE	3.15	<0.35
Penicilloyl V IgE	2.77	<0.35
Ampicillin IgE	<0.35	<0.35
Amoxicillin IgE	<0.35	<0.35
Total serum IgE	186	0–114

Given the patient's history, these results were considered to be confirmatory of penicillin allergy based on the presence of specific IgE to penicilloyl (penicillin allergenic determinant). Even without specific IgE to ampicillin and amoxicillin antigens, a patient may still have anaphylaxis to these drugs by virtue of the presence of specific IgE to penicilloyl.³ Also, blood testing was performed 12 days after the anaphylactic event; therefore, because of anaphylactic consumption of IgE, the specific IgE titers may have been lower than they would have been had they been measured before the event or at a much later date.

DISCUSSION

A number of salient points are raised by this case. First, patients can develop severe IgE-mediated allergy to penicillin despite having safely received penicillins in the past. We were able to find one other case of a woman who had previously received amoxicillin without incident but then developed intrapartum anaphylaxis thought to be due to penicillin, which led to fetal brain damage.⁵ However, specific penicillin testing to confirm penicillin allergy was not performed. This woman was not described as having any underlying medical conditions. In our case, it is possible that the altered immunological status associated with RA and/or treatment with immunomodulatory agents played some role in the development of penicillin sensitivity.

It is unclear how the altered immunological status associated with an autoimmune disease such as RA would affect the development of specific IgE synthesis to a drug. However, recent evidence has shown that T_H1 diseases, including RA specifically, can coexist with T_H2 allergic disease.^{6,7} We found no data on whether immunomodulatory drugs such as etanercept and adalimumab can affect the mechanism of IgE sensitization.

One could hypothesize that the immunological changes associated with pregnancy may have played a role in the development of new sensitivity to penicillin (with the sensitization occurring during the first trimester with the course of amoxicillin) and/or made her more prone to a severe anaphylactic presentation with subsequent exposure. Little has been reported about the effects of pregnancy on development of new allergic sensitization to a drug. However, normal pregnancy is known to be associated with an increased T_H2 response, including increased interleukin 4 and interleukin 10 production, increased immunoglobulin production, and de-

creased T_H1 response.^{8–10} A T_H2 profile (with production of cytokines such as interleukin 5, interleukin 4, and interleukin 13) is known to induce IgE synthesis.¹¹ It is also well known that women with allergic disease, particularly asthma, can have a worsening of disease during pregnancy.¹²

As far as the occurrence of pregnancy in a woman with an autoimmune disease such as RA, even less is known about the effects on development and manifestation of IgE-mediated hypersensitivity. Ostensen¹³ reported that pregnancy temporarily ameliorates the symptoms of RA in approximately 75% of pregnant patients. He hypothesized that the shift from T_H1 to T_H2 immune response during pregnancy, including increased production of interleukin 4 and interleukin 10, may ameliorate the T_H1 -driven symptoms of RA. Munoz-Valle et al¹⁴ found that pregnant women with RA have a pronounced degree of T_H2 response compared with healthy pregnant women (in whom it was not seen). It is hypothetically possible that the combined immunological environment of pregnancy on top of RA may enhance the chance of developing new drug allergy, with severe anaphylactic reaction if exposed again to the drug during the pregnancy.

The second point is that unexpected severe intrapartum anaphylaxis can occur, and it can be life threatening to the mother or fetus. Labor and delivery teams should be prepared for the possibility of such reactions. One could make the argument that all pregnant women with group B streptococcus should be screened for penicillin allergy regardless of history, but cost-effectiveness studies would be needed.

The third point is that safe and reliable methods for diagnosis of penicillin allergy must be available. The gold standard for diagnosing drug allergy involves direct challenge with the drug, but in cases such as this, a direct drug challenge may be unsafe. The major and minor allergenic determinants of penicillin have been established, and skin testing using these reagents is considered more reliable than available in *in vitro* assays for penicillin specific IgE, such as the Pharmacia ImmunoCAP radioallergosorbent test fluorescent enzyme immunoassay.¹⁵ Skin testing using both major and minor determinants has a specificity as high as 98% to 99%.^{1,3} However, the only US manufacturer of the penicillin major determinant, benzylpenicilloyl-polylysine (PrePen), ceased production of the reagent in 2004,^{1,3} and the minor determinants have never been commercially available in the United States. *In vitro* tests confirm a positive skin test result in only approximately 40% of cases.^{16,17} Clearly, the lack of availability of Food and Drug Administration–approved skin testing reagents in the United States can be considered a major public health problem, as discussed elsewhere.¹⁸ However, this case illustrates that during the current time of commercial unavailability of the skin testing reagents, a positive result on the ImmunoCAP assay can be helpful in confirming penicillin allergy in cases in which direct drug challenge is deemed unsafe.

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