

CASE REPORT

Diffuse maculopapular exanthema and a positive lymphocyte transformation test reaction in response to clarithromycin

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Abstract

Macrolides are one of the most widely used antibiotics, but the mechanisms underlying macrolide allergy have not been clearly elucidated. Diffuse maculopapular exanthema caused by clarithromycin is extremely rare, of which clinical images have not been reported. Here, we report a case of a 55-year-old Japanese female who was treated with oral clarithromycin and lysozyme hydrochloride due to odontogenic maxillary sinusitis. On the 15th day after starting both drugs, she suffered from diffuse maculopapular exanthema, which worsened despite the discontinuation of lysozyme hydrochloride and the introduction of treatment with oral and topical corticosteroids and oral levocetirizine. Clarithromycin was discontinued and an intravenous corticosteroid introduced on the 19th day. A lymphocyte transformation test was positive for clarithromycin but negative for lysozyme hydrochloride. Although adverse effects of clarithromycin are extremely rare, physicians should be aware of clarithromycin as a potential cause of a type IV allergic reaction.

INTRODUCTION

Macrolide antibiotics, commonly referred to as macrolides, are one of the most widely used antibiotic groups and have a well-established role in treating a broad range of common pathogens, including upper and lower respiratory infections, gastric infection and certain sexually transmitted diseases. Since 14-membered (erythromycin and clarithromycin) and 15-membered macrolides (azithromycin) possess anti-inflammatory and immunomodulatory properties, long-term macrolide treatment is effective for chronic rhinosinusitis and chronic respiratory diseases such as diffuse panbronchiolitis, cystic fibrosis, asthma and chronic obstructive pulmonary disease [1–3]. Clarithromycin is the most frequently prescribed oral macrolide antibiotic [1, 4].

In addition to their clinical efficacy, macrolides are among the safest antibiotics based on epidemiological studies, and allergic

reactions to them occur in only 0.4–3% of treatments. In particular, clarithromycin allergy is rarer than allergy to other macrolides [1]. However, the mechanisms underlying macrolide allergy have not been clearly elucidated [1, 4, 5]. To better understand adverse reactions caused by clarithromycin, here, we report a case of a 55-year-old Japanese female with diffuse maculopapular exanthema caused by clarithromycin. To the best of our knowledge, this is the first case report of diffuse drug eruption with a positive lymphocyte transformation test (LTT) reaction to clarithromycin, suggesting that a delayed allergic reaction mediated by T cells, not immunoglobulin E (IgE), may have been induced.

CASE REPORT

A 55-year-old Japanese female was referred to an oral surgery specialist by an otolaryngologist due to refractory, chronic

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rhinosinusitis. She had been treated with 300 mg/day of cefteram pivoxil and as needed use of 660 mg of acetylsalicylic acid. The oral surgeon diagnosed odontogenic maxillary sinusitis and initiated macrolide treatment with 400 mg/day of oral clarithromycin and 90 mg/day of oral lysozyme hydrochloride, a mucolytic agent. On the 14th day after starting oral administration of both drugs, the oral clarithromycin was reduced to 200 mg/day.

On the 15th day, she was referred to our division of internal medicine and dermatology. At our office visit, she had papules and erythemas on her extremities, the sides of her chest, her lower abdomen and her buttocks without mucosal affection (data not shown). Drug eruption was suspected, and lysozyme hydrochloride was discontinued because allergic reactions associated with the use of macrolides are uncommon [1]. She was treated with topical corticosteroid (0.05% betamethasone butyrate propionate) and oral levocetirizine along with 2-day oral corticosteroid (1.5 mg/day of betamethasone). Since the pruritic, maculopapular eruptions were exacerbated, she returned to our office on the 19th day (Fig. 1).

The laboratory results at the second visit to our office were as follows (normal ranges in brackets): white blood cell count 5000/ μ L (3500–9700/ μ L) (eosinophils 6.0% (0–7.0%) of white blood cell count), aspartate aminotransferase 17 U/L (13–33 U/L), alanine aminotransferase 13 U/L (8–42 U/L), lactate dehydrogenase 185 U/L (119–229 U/L), γ -glutamyl transpeptidase 12 U/L (10–47 U/L), alkaline phosphatase 167 U/L (115–359 U/L), total bilirubin 0.60 mg/dL (0.19–1.10 mg/dL), urea nitrogen 18.9 mg/dL (8–22 mg/dL), creatinine 0.61 mg/dL (0.31–0.89 mg/dL) and IgE 57 IU/mL (0–170 IU/mL).

Clarithromycin was discontinued, and she was treated with an additional, intravenous corticosteroid (40 mg of prednisolone). Then, 2.0 mg/day of oral betamethasone was used for 3 days. The pruritic erythemas disappeared with pigmentation ~1 month after the discontinuation of clarithromycin and oral betamethasone, although the patient went on with levocetirizine and topical corticosteroids tapering off to 0.1% dexamethasone propionate.

The patient's consent of oral provocation test (OPT) as well as skin testing and skin biopsy could not be obtained after hypersensitivity reactions including anaphylaxis, Stevens–

Johnson syndrome, hepatitis or renal failure possibly induced by OPT were informed. We offered an early LTT to determine her possible allergen(s), which was accepted. Positive and negative LTT reactions to clarithromycin (stimulation index 3.46; normal <1.8) and lysozyme hydrochloride (stimulation index 1.54) were obtained using blood samples taken 7 days after discontinuation of the oral corticosteroid. The patient was finally diagnosed with diffuse maculopapular drug eruption probably caused by clarithromycin.

DISCUSSION

Drug hypersensitivity reactions (DHRs) are defined as adverse effects of drugs that clinically resemble allergic reactions. When an immunological mechanism, i.e. a drug-specific antibody or T cell, is demonstrated for the reactions, the DHRs are considered allergic [6]. DHRs are clinically classified as either immediate DHRs such as urticaria, angioedema, bronchospasm, gastrointestinal symptoms, and anaphylaxis, or delayed DHRs such as maculopapular eruptions, fixed drug eruptions, Stevens–Johnson syndrome and effects on internal organs, including hepatitis and renal failure. Mechanistically, DHRs are defined as allergic and non-allergic. The most common allergies are caused by IgE- and T cell-mediated reactions [6].

Since the patient presented here showed diffuse maculopapular exanthema 15 days after the start of clarithromycin and a positive LTT that implied the stimulation of drug-specific T cell clones [7], clarithromycin may induce T cell-mediated, delayed allergic DHRs [6]. Although LTT was performed 7 days after discontinuation of an oral corticosteroid at the request of the patient, it would have been better to perform LTT at least 4 weeks after treatment with corticosteroids [1, 6]. Therefore, the positivity of LTT would have been higher at the time of the examination. Further, the patient was reluctant for OPT, skin patch and intradermal testing, and skin biopsy, which would have been useful investigations to have performed [1, 4–6]. Considering that LTT would not be a completely validated technique [1, 6], lack of these diagnostic tests is a limitation in the case report.

In the literature, diffuse maculopapular exanthema caused by clarithromycin is extremely rare, even compared to reactions to other macrolides [1]. Only one previous case had been published: a patient with an allergy to β -lactam antibiotics, which may cause IgE-mediated allergic reactions [5, 6], also showed DHRs to clarithromycin [8]. Since the patient had both lip angioedema and maculopapular rash 6 days after the start of clarithromycin [8], allergic mechanisms of types I (IgE-mediated) and IVb (Th2-mediated; eosinophilic infiltration) might be involved [5, 6]. Further, since the patient had allergic symptoms within 3 h after OPT with clarithromycin, a type I allergy might be mainly involved [5, 6].

A recent topic regarding adverse effects of clarithromycin is whether clarithromycin is associated with an increased risk of cardiovascular events and death [9, 10]. Although the risk of cardiovascular events and death is still controversial, an epidemiologic study indicated no increased risk of cardiovascular death in a general outpatient population but a transiently increased risk of cardiovascular death during Days 0–7 after treatment with clarithromycin [10], speculating that allergic response(s) might be involved in addition to non-allergic mechanism(s).

In conclusion, while adverse effects of treatment with clarithromycin are considered to be extremely rare, clarithromycin may induce types I and IV immune responses. The case of this patient illustrates the importance of physician awareness of

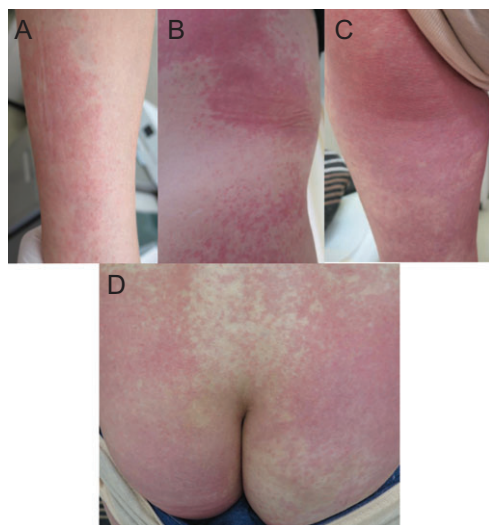


Figure 1: Clinical features of the patient on the second visit to the division of internal medicine and dermatology. Diffuse papules and erythemas on the left forearm (A), right flank region (B), left thigh (C) and buttocks (D).

clarithromycin as a potential cause of a type IV allergic reaction.

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CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ETHICAL APPROVAL

No ethical approval was required as this was a clinical case.

CONSENT

Patient permission was obtained prior to writing this report.

GUARANTOR

Dr Toshiki Ito.

REFERENCES

1. Araújo L, Demoly P. Macrolides allergy. *Curr Pharm Des* 2008; **14**:2840–62. DOI:10.2174/138161208786369812.
2. Gotfried MH. Macrolides for the treatment of chronic sinusitis, asthma, and COPD. *Chest* 2004; **125**:52S–61S. DOI:10.1378/chest.125.2_suppl.52S.
3. Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. *Eur Respir J* 2013; **42**: 239–51. DOI:10.1183/09031936.00136712.
4. Mori F, Barni S, Pucci N, Rossi E, Azzari C, de Martono M, et al. Sensitivity and specificity of skin tests in the diagnosis of clarithromycin allergy. *Ann Allergy Asthma Immunol* 2010; **104**:417–9. DOI:10.1016/j.anai.2010.03.010.
5. Gruchalla RS, Pirmohamed M. Clinical practice. Antibiotic allergy. *N Engl J Med* 2006; **354**:601–9. DOI:10.1056/NEJMcp043986.
6. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International consensus on drug allergy. *Allergy* 2014; **69**:420–37. DOI:10.1111/all.12350.
7. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy* 2004; **59**: 809–20. DOI:10.1111/j.1398-9995.2004.00547.x.
8. Igea JM, Lázaro M. Hypersensitivity reaction to clarithromycin. *Allergy* 1998; **53**:107–9. DOI:10.1111/j.1398-9995.1998.tb03787.x.
9. Berni E, de Voogd H, Halcox JP, Butler CC, Bannister CA, Jenkins-Jones S, et al. Risk of cardiovascular events, arrhythmia and all-cause mortality associated with clarithromycin versus alternative antibiotics prescribed for respiratory tract infections: a retrospective cohort study. *BMJ Open* 2017; **7**:e01398. DOI:10.1136/bmjopen-2016-013398.
10. Inghammar M, Nibell O, Pasternak B, Melbye M, Svanström H, Hviid A. Long term risk of cardiovascular death with use of clarithromycin and roxithromycin—a notional wide cohort study. *Am J Epidemiol* 2018; **187**:777–85. DOI:10.1093/aje/kwx359.