

## Oral bullous lesions due to the azithromycin intake

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### CASE STUDY

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### ABSTRACT

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We report a case of 29-year-old woman who was admitted to our Department with red eyes and two bullae located on the right buccal mucosa. Otherwise she is healthy but one day before she finished azithromycin (Sumamed, Tewa, Croatia) intake as she had pneumonia. Direct and indirect immunofluorescence did not reveal presence of vesiculobullous disorders. During the period of nine days she was given 40mg of prednisone (Decortin, Merck, Germany) orally as well as betamethasone (Beloderm, Belupo, Croatia) in orabase locally and after that the lesions subsided.

#### Key Words

Azithromycin, antibiotic, bullous lesions, drug reaction, adverse, oral reaction

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#### Implications for Practice:

##### 1. What is known about this subject?

Adverse drug reactions may occur after only one dose of the

drug or taking the drug for a longer period of time.

##### 2. What new information is offered in this case study?

Azithromycin has long elimination half-time which allows an allergic reaction to occur even after cessation of drug use.

##### 3. What are the implications for research, policy, or practice?

In case macrolide allergy occurs, the treatment of choice is to avoid further use of the single causal macrolide.

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### Background

Every medication has the potential to lead to the adverse reaction in the body. Also, adverse reactions (ADRs) to medications might develop on every system of the body. The offending drug might lead to the ADRs after only one dose has been taken or patient might take drug for many years and then ADRs might evolve. Data from the literature suggest that non-steroidal antiinflammatory drugs and antibiotics most frequently lead to such reactions.<sup>1</sup> Among antibiotics, penicillin and sulphonamides are known to induce unwanted side-effects more frequently than other antibiotics. Richa et al.<sup>2</sup> based on the results of his study, stated that the most common antibiotic resulting in ADRs was injection of ceftriaxone (35.71 per cent), followed by azithromycin tablet (7.39 per cent), ofloxacin+ornidazol (5.35 per cent), ofloxacin (3.57 per cent), ciprofloxacin (2.29 per cent), amoxicillin (2.55 per cent), cefixime (2.29 per cent), and linezolid injection (2.04 per cent). Most commonly ADRs were on the skin (47.44 per cent), gastrointestinal system (39.28 per cent), central nervous system (5.35 per cent), cardiovascular system (3.57 per cent) and renal and genitourinary system (1.78 per cent). Uchit et al.<sup>3</sup> reported on the sample of 2639 total adverse drug reactions that 1315 (49.82 per cent) were due to antimicrobial agents, mostly to cotrimoxazole (19.54 per cent), ampicillin (18.25 per cent), rifampicin (6.6 per cent) and azithromycin (5.3 per cent). It is well-known that hypersensitivity reactions to macrolides are rare.<sup>4</sup>

## Case details

The 29-year-old woman was admitted to the Department of oral medicine, School of Dentistry in Zagreb. Clinical examination revealed that she had red eyes and two bullae located on the right buccal mucosa (Figure 1). Detailed medical history was unremarkable. However, one day before she was admitted she finished azithromycin therapy (Sumamed, Tewa, Croatia) as she had pneumonia. Azithromycin was swallowed one tablet of 500mg a day during the period of three days (3 tablets × 500mg in total). She did not take any other medications and she denied previous food allergies or consumption of new food. A biopsy specimen of the buccal mucosa was taken. Direct immunofluorescence finding did not reveal deposits of immunoglobulins or complement. Indirect immunofluorescence finding did not reveal circulating antibodies of pemphigus or bullous pemphigoid. These negative findings excluded autoimmune blistering diseases. The patient's laboratory tests were within normal range. Her eyes were red probably because they were also affected with allergy, in a kind of mild Stevens-Johnson syndrome (i.e., without involvement of other mucosae). She was prescribed 40mg of prednisone (Decortin, Merck, Germany) orally as well as betamethasone (Beloderm, Belupo, Croatia) in orabase locally which she applied four times a day. After nine days the lesions subsided. The patient did not have any lesions three months after this eruption.

## Discussion

Within published literature, many adverse effects due to azithromycin are reported on the various organs, mainly on the cardiovascular system but also on the gastrointestinal.<sup>5</sup>

However, regarding dermatological disturbances Nappe et al.<sup>6</sup> reported in the year 2016 that azithromycin is not frequently associated with SJS, toxic epidermal necrolysis or other cutaneous reactions. Our Pubmed search revealed only few adverse reactions to azithromycin on the skin. Das et al.<sup>7</sup> described a case of azithromycin-induced bullous fixed drug eruption. Zweegers and Bovenschen<sup>8</sup> described acute and painful perioral pustular dermatosis erupted one day after the patient had taken azithromycin for a throat infection. Bauer et al.<sup>9</sup> described a patient fever, cutaneous eruption, eosinophilia, and hypotension after azithromycin intake. Pereira et al.<sup>10</sup> reported acute onset of widespread pustular eruption after the patient has taken azithromycin. Schmutz et al.<sup>11</sup> reported Stevens-Johnson syndrome as a result of azithromycin intake. Da Cunha Filho et al.<sup>12</sup> reported acute generalized exanthematous pustulosis by azithromycin. Sriratanaviriyakul et al.<sup>13</sup> reported systemic

symptoms syndrome (DRESS) associated with azithromycin and presenting like septic shock. A skin biopsy showed evidence of spongiotic lichenoid dermatitis with eosinophils and neutrophils, compatible with a systemic drug-induced hypersensitivity reaction. The same finding was reported by Bauer et al.<sup>9</sup> Rajaii et al.<sup>14</sup> reported a case of acute generalized exanthematous pustulosis due to the azithromycin therapy. Recently, case of SJS after the completion of five days azithromycin was described.<sup>15</sup>

To our knowledge this is the second case upon solely oral reaction to azithromycin in the so far published literature. We reported first case upon oral bullous reaction due to the azithromycin in the year 2011. It is interesting to note that patients developed lesions after three days of azithromycin intake which was upon completion of the therapy. This was also reported by others<sup>5,15</sup> and might be due to the fact that azithromycin remains at therapeutic concentrations during ten days after the cessation of therapy.

The only one hundred per cent sure test for diagnosing reaction to drugs is rechallenge with the offending drug<sup>4</sup> which is not ethical, therefore it was not performed in our patients.

## Conclusion

In this case differential diagnosis was cicatricial or bullous pemphigoid, multiform exudative erythema and chronic bullous disease in children.

Last but not least, patients with such reactions should be strongly advised not to take azithromycin again as fatal anaphylactic shock might develop.

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## References

1. Boras VV, Andabak-Rogulj A, Brailo V, et al. Adverse drug reactions in the oral cavity. *Acta Clin Croat.* 2015;54(2):208–15.
2. Richa, Tandon VR, Sharma S, et al. Adverse drug reactions profile of antimicrobials: A 3-year experience, from a tertiary care teaching hospital of India. *Indian J Med Microbiol.* 2015;33(3):393–400.
3. Uchit GP, Shrivastava MP, Badar VA, et al. Adverse drug reactions to antimicrobial agents in a tertiary care hospital in Nagpur. *J Indian Med Assoc.* 2012;110(4):224–7.
4. Ünal D, Demir S, Gelincik A, et al. Diagnostic value of oral challenge testing in the diagnosis of macrolide hypersensitivity. *J Allergy Clin Immunol Pract.* 2017;S2213-2198(17)30520–2.
5. Loncar B, Mravak-Stipetic M, Skerlev M, et al. Bullous

oral eruptions caused by azithromycin. *Acta Stomatol Croat.* 2011;45(2):120–124.

6. Nappe TM, Goren-Garcia SL, Jacoby JL. Stevens-Johnson syndrome after treatment with azithromycin. An uncommon culprit. *Am J Emerg Med.* 2016;34:676.e1–676.e.3.
7. Das A, Sancheti K, Podder I, et al. Azithromycin induced bullous fixed drug eruption. *Indian J Pharmacol.* 2016;48(1):83–5. doi: 10.4103/0253-7613.174565.
8. Zweegers J, Bovenschen HJ. A woman with skin abnormalities around the mouth. *Ned Tijdschr Geneesk.* 2012;156(46):A4613.
9. Bauer KA, Brimhall AK, Chang TT. Drug reaction with eosinophilia and systemic symptoms (DRESS) associated with azithromycin in acute Epstein-Barr virus infection. *Pediatr Dermatol.* 2011;28(6):741–3.
10. Pereira A, Pinho Â, Sousa P, et al. Acute onset of widespread pustular eruption. *Aust Fam Physician.* 2015;44(6):379–81.
11. Schmutz JL, Barbaud A, Trechot P. Azithromycin and Stevens-Johnson syndrome. *Ann Dermatol Venereol.* 2005;132(8-9 Pt 1):728.
12. da Cunha Filho RR, Bordignon SC, Cassol M, et al. Acute generalized exanthematous pustulosis by azithromycin. *Int J Dermatol.* 2015;54(6):e247–9.
13. Sriratanaviriyakul N, Nguyen LP, Henderson MC, et al. Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) syndrome associated with azithromycin presenting like septic shock: a case report. *J Med Case Rep.* 2014;8:332.
14. Rajaii RM, Payne KS, Malters JM, et al. Acute generalized exanthematous pustulosis reported due to loxosceles envenomation may be secondary to azithromycin therapy. *Mo Med.* 2014;111(3):186.
15. Mancano MA. ISMP Adverse Drug Reactions: Acute Disseminated Intravascular Coagulation Due to Oxaliplatin Azithromycin-Induced Stevens-Johnson Syndrome Acute Jugular Vein Thrombosis with Rituximab Hemorrhagic Bullae of the Fingers Induced by Furosemide. *Hosp Pharm.* 2017;52(1):13–16.

## PEER REVIEW

Not commissioned. Externally peer reviewed.

## CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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## PATIENT CONSENT

This submission is compliant. The authors, *Vučičević Boras V, Lončar Brzak B, Lakoš Jukić I, Ljubojević Hadžavdić S, Negovetić Vranić D, and Pelivan I*, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. with the requirements of local research ethics committees.

**Figure 1: Bullous eruption on right buccal mucosa**

