Azithromycin-Related Agranulocytosis in an Elderly Man with Acute Otitis Media

Tomohiro Kajiguchi and Toshihito Ohno

Abstract

Azithromycin (AZM) is widely used for respiratory tract infections and otitis media because of its activity against *Haemophilus influenzae* and atypical pathogens, and its ease of administration. Although leukopenia is the one of the most frequent AZM-related laboratory abnormalities in children, agranulocytosis has not been reported in adults. Here, we present the case of an 81-year-old man with agranulocytosis following AZM-treatment for acute otitis media. He developed febrile neutropenia and granulocyte colony-stimulating factor and cefepim were administered. All his symptoms and absolute neutrophil counts were recovered within 7 days after admission. Physicians must be vigilant in identifying drug-induced neutropenia in AZM-treated patients because early detection can decrease the severity and prevent mortality.

Key words: azithromycin, agranulocytosis, febrile neutropenia

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Introduction

Agranulocytosis is a potentially life-threatening hematological condition of acute onset in which the number of circulating neutrophils falls to less than 500/mm³. Even with the advent of granulocyte colony-stimulating factors and new antibiotics, this disorder leads to an increased risk of bacterial infections and sepsis, resulting in a case-fatality rate of approximately 5-15% (1, 2). Azithromycin (AZM) is a macrolide antibiotic, structurally modified from erythromycin and noted for its activity against some gram-negative organisms particularly *Haemophilus influenzae* (3-5). Because of its ease of administration and 3-day duration of therapy, together with its good gastrointestinal tolerability, AZM is widely used for un-complicated otitis media and respiratory tract infections in adults and children. Here, we present an 81-year-old man who developed agranulocytosis after 3-day administration of AZM for acute otitis media.

Case Report

An 81-year-old Japanese man presented to his physician with otalgia and febricula and the doctor diagnosed acute otitis media. His medical history included hypertension and prostatomegaly, for which valsartan (80 mg/day) and naftopidil (75 mg/day) were administered for 6 years, respectively. He was treated with AZM-monotherapy (500 mg/day for 3 days) but no improvement of symptoms was seen. Six days later, fever persisted and blood examination showed a sudden drop in white blood cell (WBC) count (6,600 to 1,100/mm³) and elevation of C-reactive protein (CRP: 7.6 mg/dL). Therefore, he consulted the Hematology and Oncology Branch of our hospital and was admitted for intensive treatment. On admission (day 0), blood examination showed a WBC count of 1,600/mm³, an absolute neutrophil count (ANC) of 96/mm³, a hemoglobin level of 11.1 g/dL, a platelet count of 17.8×10⁴/mm³, a CRP level of 10 mg/dL. The changes in WBC and ANC over time are shown in Fig. 1. Bone marrow examination showed a remarkable decrease of myeloid precursors. CT scan examination revealed the presence of fluid collection of left tympanic cavity and mastoid, suggesting otitis and mastoiditis. Because of febrile neutropenia, granulocyte colony-stimulating factor (G-CSF) (filgrastim: 75 μg/day) and cefepim (4 g/day) were immediately administered. Duration of drug-administration was 3 days (filgrastim: day 0 to 2) and 5 days (cefepim: day 0 to 4), respectively. Fever was resolved on the following
day (day 1) and ANC count recovered to 4,704/mm$^3$ on day 7. Because all symptoms improved, the patient was discharged. The patient has been well and no recurrence of agranulocytosis was seen.

**Discussion**

Although clinical studies have demonstrated that AZM has no major or consistent effect on laboratory safety parameters, the incidence of treatment-related abnormalities in blood cell count, particularly leukocyte/neutrophil, has been reported (6-8). Higa and Saito reported that leukopenia and neutropenia was observed in eleven (0.88%) and in two (0.22%) adults patients in clinical trial in Japan. All these abnormalities were reported to be mild and transient. On the other hand, leukopenia occurred more often in children. Thirty-three patients (7.47%) had a decrease of leukocyte counts, however, no case had a severe leucopenia (8). The incidence of laboratory abnormalities caused by AZM and the other comparator antimicrobial agents (penicillins, penicillin derivatives, cephalosporins, and macrolides) in worldwide clinical trials was analyzed (6, 7). In this report, the incidence of neutrophil count abnormality, one of the most frequent AZM-related laboratory abnormalities, was observed in 1.5% of adults and 1.9% of children, and there was no significant difference between AZM and comparator (7). In adult patients, the significance of the changes in neutrophil count was not clear; most patients had reduced neutrophil counts, but some developed neutrophilia (6). In the present case, agranulocytosis seemed to be closely related to AZM because no drug other than AZM was administered for otitis media, and neutropenia developed just after the administration of AZM. To our knowledge, no case of AZM-related agranulocytosis in an adult patient has been reported. Idiosyncratic drug-induced agranulocytosis is a rare disorder with an incidence of 2.4-15.4 cases per million (9). Currently, this disorder remains a potential serious adverse event due to the frequency of severe sepsis and septic shock in approximately two-thirds of all hospitalized patients (2, 10).

In conclusion, we present the first documented case of AZM-related agranulocytosis in an adult patient. Physicians must pay careful attention to identifying drug-induced neutropenia in AZM-treated patients because early detection can decrease the severity and prevent mortality.

**References**


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