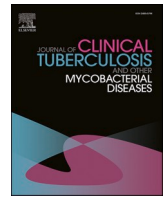




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## Case Report

# Azithromycin: A promising treatment option for *Mycobacterium avium* complex pulmonary disease in case of intolerance to clarithromycin

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## ABSTRACT

Macrolide-based combination chemotherapy is recommended for the treatment of *Mycobacterium avium* complex (MAC) pulmonary disease (MPD). The susceptibility of the MAC to macrolide antibiotics (MAs) determines the efficacy of treatment and clinical course of MPD. However, MAs cause several adverse effects, resulting in the discontinuation of macrolide-based combination chemotherapy. We encountered two women aged 65 years and 66 years diagnosed with MPD based on bronchoscopic examinations. They were initially treated with clarithromycin-based combination chemotherapy. However, neither patient could continue with chemotherapy owing to adverse events such as rash and edema. We switched clarithromycin with azithromycin, and the patients were able to continue chemotherapy without adverse events. Both patients completed their treatment successfully. Azithromycin, which also belongs to the class of MAs, can be a promising therapeutic option for MPD in case of clarithromycin intolerance.

## 1. Introduction

Recently, the incidence rate of nontuberculous mycobacterial (NTM) pulmonary diseases has increased globally [1]. *Mycobacterium avium* complex (MAC) is one of the most frequently isolated causative agents of NTM pulmonary disease in the world [2].

Macrolide-based combination chemotherapy, in conjunction with ethambutol (EB) and rifampicin (RFP), is recommended for the treatment of MAC pulmonary disease (MPD) [3,4]. The macrolide antibiotics (MAs) chosen for this purpose are mainly clarithromycin (CAM) and azithromycin (AZM). Studies have shown an association between the in vitro sensitivity tests for MAs and the clinical course of MPD [5,6]. Therefore, MAs should be included in the combination chemotherapeutic regimen if possible, after confirming the susceptibility of the causative organisms. However, MAs can often cause several adverse effects, such as gastrointestinal symptoms and cardiovascular toxicity [7]. The inability to administer MAs to a patient with MPD, in the event of adverse events or intolerance, is a great disadvantage. Herein, we report the cases of two patients with MPD who were successfully treated

with AZM-based combination chemotherapy, owing to the inability to continue with CAM because of adverse events.

## 2. Case report

### 2.1. Patients 1 and 2

Two Japanese women aged 65 years and 66 years were referred to our hospital with a complaint of chronic cough. Both patients were slender with body mass indices of 17.1 and 19.0, respectively. Neither patient had a history of smoking or alcohol consumption. The chest computed tomography (CT) scan of patient 1 revealed opacities with small nodules in the middle lobe and a small opacity near the border between the middle and lower lobes. The chest CT of patient 2 revealed patchy opacities in the middle lobe and lingular segment and small peripheral pulmonary nodules along the bronchovascular bundle, in addition to bronchiectasis in the lower left lobe (Fig. 1A, B). The findings of laboratory examination in both patients were almost normal, except for a mild elevation in the erythrocyte sedimentation rate.

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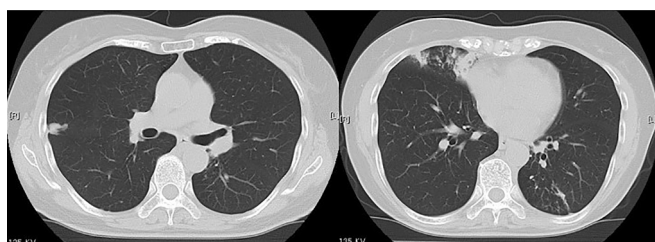
Bronchoscopic examination was performed for the following reasons: patient 1 did not have any productive cough; patient 2, repeated spontaneous sputum examinations, such as bacteriology and cytology, did not facilitate a definite diagnosis in patient 2. Bronchoalveolar lavage fluid samples obtained from both middle medial lobes (patient 1) and inferior lingular bronchus (patient 2) were strongly positive for acid-fast bacilli. Both patients also tested positive for MAC on the polymerase chain reaction test. Moreover, *M. avium* was subsequently isolated from the bronchoalveolar lavage fluid samples of both patients. Both patients were diagnosed with MPD, which was classified as the nodular bronchiectasis type, based on the American Thoracic Society/European Respiratory Society criteria [3]. Both patients were initially administered combination therapy with CAM (400 mg, twice daily), rifampicin (RFP (450 mg, once daily), and EB (1000 mg and 750 mg, once daily, respectively). However, rashes appeared on the skin of the face and trunk 7 days after starting treatment in patient 1 and bilateral pretibial edema extending to the dorsum of the feet appeared 7 days after the initiation of treatment in patient 2, which gradually worsened with the progression of treatment. We suspected that these findings were the adverse effects caused by the antimicrobial agents, which were stopped immediately. The rashes in patient 1 and the pretibial edema in patient 2 disappeared rapidly. We considered CAM to be the cause of the skin eruptions and pretibial edema because the challenge test with only CAM at the same dose reproduced the same skin rash on the fifth day in patient 1, and the result of the drug-induced lymphocyte stimulating test was positive for CAM in patient 2. Since both patients could not tolerate the drug, we administered AZM (250 mg, once daily), instead of CAM, in combination with RFP and EB. The results of drug susceptibility testing for *M. avium* isolated from patient 1 and patient 2 are shown in Table 1. The symptoms improved after 4 weeks of AZM-based chemotherapy in patient 1 and after 7 weeks in patient 2, without the occurrence of adverse events, including rash and edema. Chemotherapy was successfully continued for 15 months in patient 1 and 13 months in patient 2. Chest CT scans performed after the completion of chemotherapy revealed significant improvement in the mycobacterial foci in their lungs (Fig. 2). The QT intervals of both patients, which were carefully monitored with regular electrocardiography, remained unchanged throughout their respective treatments.

We obtained written informed consent from the patients for the publication of this report.

### 3. Discussion

Our study provided evidence that AZM can be a promising therapeutic option for MPD in patients who cannot tolerate CAM.

In contrast to several other countries, the use of AZM for MPD had not been approved until 2021 in Japan and until 2011 in South Korea [8]. Prior to 2011, many clinical studies on the use of CAM and AZM for treating MPD were published, primarily from Western countries. Thus, it is believed that Japan and South Korea were late to approve AZM for treating MPD. Consequently, there are only a few reports on the efficacy and safety of AZM in patients with MPD in Japan.



**Table 1**  
Antimicrobial susceptibility profile and *Mycobacterium avium* isolated from bronchoalveolar lavage fluid of two cases.

Antimicrobial Agents	Case 1		Case 2	
	MIC	Category	MIC	Category
Streptomycin	32	R	4	I
Ethambutol	64	R	8	R
Kanamycin	64	R	4	I
Rifampicin	0.06	S	1	I
Rifabutin	0.03	I	0.25	I
Levofloxacin	8	R	0.5	S
Clarithromycin	0.5	S	1	S
Ethionamide	16	R	4	I
Amikacin	16	R	4	I

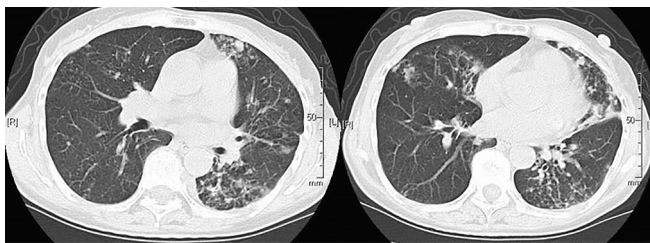
Abbreviation: MIC, minimum inhibitory concentration

The frequency of adverse effects due to AZM and CAM, as shown by individual studies of the two drugs, are comparable (AZM vs CAM. nausea, 2.6% vs 3.8%; diarrhea, 3.6% vs 3.0%; abdominal pain, 2.5% vs 1.9%, and head ache, 1.3% vs 1.7%) [9,10]. However, during the treatment of MPD, AZM showed a lower frequency of adverse events that discontinued treatment compared to CAM [8]. Furthermore, it is suggested that AZM has fewer drug interactions with co-prescribed medications than CAM. In general, drugs are metabolized by cytochromes and drug transporters in the liver. These influence the serum concentration of co-prescribed drugs [11]. CAM inhibits cytochrome P450 3A4 (CYP3A4) and organic anion-transporting polypeptide 1B1 (OATP1B1) and OATP1B3, which influence the drug plasma concentrations not metabolized by CYP3A4, while AZM shows no such effect [12,13,14]. Actually, AZM presents a lower risk of gastrointestinal bleeding than CAM when used in combination with direct oral anticoagulant [15]. AZM is preferable to CAM because of fewer drug interactions and higher likelihood of treatment continuity. Moreover, the efficacy of combination chemotherapy with CAM and AZM is similar for patients with the nodular bronchiectatic form of MPD [16].

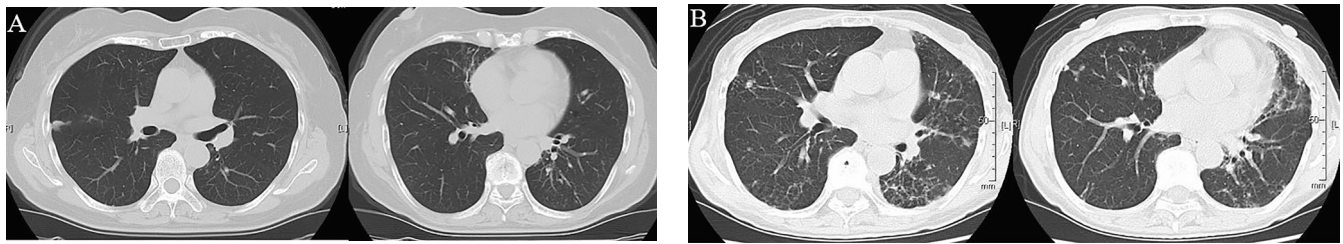
The reason why CAM caused rash and edema in our patients, and AZM did not, is uncertain. Moreover, both patients did not take any regular oral medications that could have interacted with CAM or AZM. AZM is correctly classified as an azalide owing to the presence of a 15-membered ring in its chemical structure. However, AZM is also considered to be a type of MA (possessing a 15 membered-ring) because of its structural similarity to macrolides [3,17]. Therefore, the adverse events could have been associated with the slight structural variations or the differences between the pharmacokinetics or pharmacodynamics of CAM and AZM. AZM is preferable to CAM because of low drug interaction and treatment continuity for the treatment of MPD.

### 4. Conclusion

It is possible to successfully use AZM for the treatment of MPD even in cases of adverse drug reactions or intolerance to clarithromycin. Clinicians should not discard the whole class of macrolides for the treatment of MPD because of an adverse reaction to one drug, especially



**Fig. 1.** A Chest computed tomography performed at referral (patient 1) Opacities with small nodules were observed in the middle lobe, along with a small opacity near the border between the middle and lower lobes. B Chest computed tomography performed at referral (patient 2) Patchy opacities were observed in the middle lobe and lingular segment with small peripheral pulmonary nodules along the bronchovascular bundle with bronchiectasis in the lower left lobe.



**Fig. 2.** A Chest computed tomography performed 15 months after initiating chemotherapy (patient 1) The opacities in the middle lobe almost disappeared and the opacity near the border between the middle and lower lobes was reduced. B Chest computed tomography performed 13 months after initiating chemotherapy (patient 2) Patchy opacities were observed in the middle lobe and lingular segment, while the small peripheral pulmonary nodules had almost disappeared.

if the side-effects are not serious.

## 5. Ethics statement

Written consent was obtained from the patients for publication of this case report. This work was also approved by Tohoku University Hospital Ethics Committee (Approval number CR-ER20-046).

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this manuscript.

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