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Azithromycin treatment failure in macrolide-resistant *Mycoplasma pneumoniae* pneumonia

To the Editors:

Mycoplasma pneumoniae is one of the most common bacterial causes of community-acquired pneumonia (CAP) [1]. Although most cases are mild, life-threatening diseases are also reported [2]. Clinical guidelines have recommended macrolides for treatment of community-acquired infection to target atypical organisms including *M. pneumoniae* [3] but there have been an increasing number of reports of macrolide-resistant *M. pneumoniae* isolated from clinical specimens [4]. Although there are studies suggesting poorer responses to macrolide in patients infected with macrolide-resistant strains, these are mainly limited to patients with mild disease. Here, we report a case of CAP due to macrolide-resistant *M. pneumoniae* with poor response to azithromycin but rapid resolution after tigecycline.

In October 2009, a 24-yr-old female was admitted to our hospital with a 4-day history of fever, sore throat, cough and myalgia, associated with nausea, vomitting and diarrhoea. 2 months before admission, she was hospitalised for acute pyelonephritis due to *Escherichia coli*. Otherwise, her past health was unremarkable. She traveled to Xi'an, China, for 7 days and returned to Hong Kong 10 days before the onset of symptoms. While in Xi'an, she stayed with her father, who had an episode of suspected respiratory tract infection, presenting with cough and sputum.

2 days before admission, she attended the accident and emergency department of a regional hospital in Hong Kong SAR (China). A chest radiograph showed right middle zone consolidation (fig. 1a). Her temperature was 39.4°C, blood pressure was 101/57 mmHg, pulse was 111 beats·min^{-1}, respiratory rate was 16 breaths·min^{-1} and oxygen saturation was 98% while breathing ambient air. She was discharged with amoxicillin–clavulanate (1,000 mg twice daily) and paracetamol. Because of persistent symptoms 1 day before admission,

azithromycin (500 mg once daily) and oseltamivir (75 mg twice daily) were added as treatment for CAP. RT-PCR of nasopharyngeal aspirate for influenza, collected 1 day before
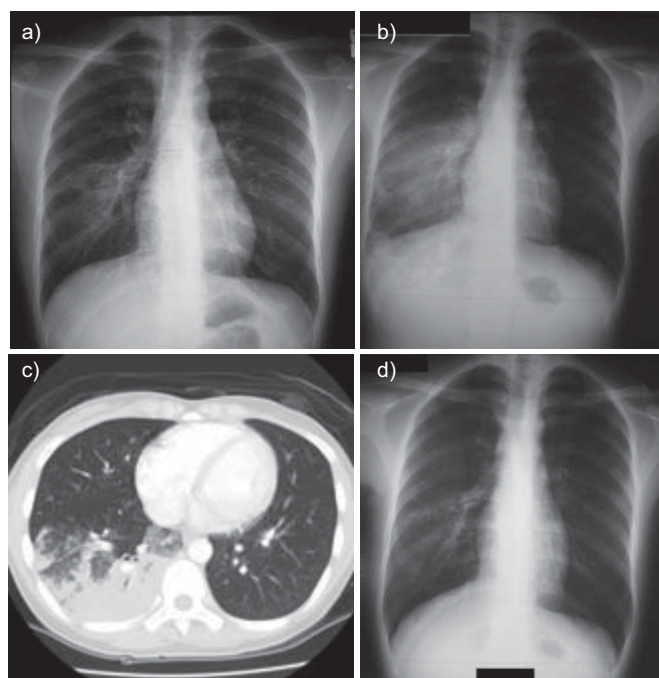

FIGURE 1. Radiographical findings. a) Chest radiograph taken 2 days before admission, showing right middle zone consolidation. b) Chest radiograph on 7th day of hospitalisation, showing progression of consolidation. c) Computed tomography on 7th day of hospitalisation, showing right lower lobe consolidation with ground-glass opacification. d) Chest radiograph on 17th day of hospitalisation, showing resolution of consolidation.

admission, was negative. Due to progression of consolidation at the right middle and lower zone, she was admitted.

After admission, there was persistent fever and further progression of lung infiltration on chest radiograph (fig. 1b), despite being given: oral azithromycin, 500 mg once daily for 9 days (day -1–8 of hospitalisation); intravenous ceftriaxone, 1 g once daily (day 2–4 hospitalisation); and piperacillin–tazobactam, 4.5 g 8-hourly (day 4–8 hospitalisation). Gram stains of sputum on admission (after 2 days of amoxicillin–clavulanate and azithromycin) revealed three or more white blood cells, one or more epithelial cells, and culture grew *Pseudomonas aeruginosa*. Ziehl–Neelsen staining for acid-fast bacilli, urine for *Legionella* antigen, nasopharyngeal aspirate immunofluorescence for influenza A and B, parainfluenza virus 1–3, adenovirus and respiratory syncytial virus, and RT-PCR for pandemic influenza H1N1 were all negative. Two sets of blood cultures were negative after 7 days of incubation. Computed tomography with contrast of the thorax was performed on day 7 of hospitalisation, which revealed right lower lobe consolidation with ground-glass opacification and small, scattered ground-glass opacities at posterior right upper lobe (fig. 1c).

Due to persistent fever and pneumonia, antibiotics were switched to intravenous tigecycline (100 mg for first dose, then 50 mg 12-hourly on day 10 of hospitalisation). There was rapid resolution of fever and improvement in lung infiltration (fig. 1d). C-reactive protein decreased from a maximum of 82.5 mg·L^{-1} (1 day before starting tigecycline) to 16.3 mg·L^{-1} (2 days after starting tigecycline). The patient was discharged on day 19 of hospitalisation.

Bronchoscopy was performed on day 10 of hospitalisation. Bronchoalveolar lavage (BAL) gave mixed growth of commensals in culture. Work-up for tuberculosis, including Ziehl–Neelsen staining and PCR for tuberculosis, were all negative. PCR for *M. pneumoniae* of the BAL (collected on day 10) and nasopharyngeal aspirate (collected on day 2) were positive, but negative for *Chlamydophila*. The bacterial DNA load in the two samples was assessed semiquantitatively by serial 10-fold dilutions of the DNA extracts. The BAL and nasopharyngeal aspirate samples remained PCR-positive up to the 10^{-3} and 10^{-2} dilutions, respectively, suggesting that the bacterial DNA load in the lower respiratory tract was higher than the upper respiratory tract. PCR for *M. pneumoniae* of the serum, collected on days 5 and 12 of hospitalisation, was negative. Paired serology, collected 10 days apart (on days 2 and 12), showed a rise of antibody titre against *M. pneumoniae* from <1:40 to 1:10,240 by particle agglutination assay, but there was no rise in antibody titre for *Chlamydia* group, *Coxiella burnetii*, influenza virus type A and B, adenovirus, parainfluenza virus type 1, 2 and 3, or respiratory syncytial virus.

Because of treatment failure, despite 9 days of azithromycin therapy, sequencing of the 23S ribosomal (r)RNA was performed. A-to-G transition at nucleotide 2,063 was found in both the nasopharyngeal aspirate and BAL, collected on days 2 and 10 of hospitalisation, respectively.

We have reported here the investigation of a case of *M. pneumoniae* pneumonia that failed to respond to prolonged azithromycin treatment. The strain was found to possess a mutation in the 23S rRNA associated with *in vitro* resistance to azithromycin and other macrolides. The finding is important because there has been a recent surge of macrolide resistance among clinical isolates of *M. pneumoniae* in some parts of the world. This rapid increase was first reported in Japan, where the incidence of macrolide-resistant strains isolated from children with *M. pneumoniae* pneumonia increased from 0% in 2002 to >30% in 2006, with a minimum inhibitory concentration (MIC) for erythromycin, clarithromycin and azithromycin, determined by microdilution methods of ⩾16 µg·mL^{-1} [4]. In a study involving Chinese children, macrolide resistance was detected in 46 out of 50 *M. pneumoniae* strains [5]. Resistance was most commonly attributed to a mutation in the domain V of the 23S rRNA. In a report from China, it was found that all macrolide-resistant strains of *M. pneumoniae* harbour an A-to-G transition mutation at position 2,063 in the 23S rRNA gene [6]. The MIC of strains with the A2063G mutation is slightly lower for azithromycin (MIC$_{90}$=64 µg·mL^{-1}) than clarithromycin or erythromycin (MIC$_{90}$ >128 µg·mL^{-1}). In Japan, other mutations in the 23S rRNA gene that resulted in high-level resistance (MIC ⩾256 µg·mL^{-1} for erythromycin and clarithromycin and 16 µg·mL^{-1} for azithromycin) include A-to-C transversion at position 2,063 and A-to-G transition at position 2,064 [7]. A C-to-G transversion at position 2,617 was also found, but this mutation was associated with low-level macrolide resistance (MIC for erythromycin, clarithromycin and azithromycin was 8, 1 and 0.031 µg·mL^{-1} respectively).

However, *in vitro* resistance does not necessarily equate to clinical failure, as demonstrated by azithromycin resistance in *Streptococcus pneumoniae* infection. Despite numerous reports of detection of macrolide-resistant *M. pneumoniae* from clinical specimens, there have been few studies on the clinical impact of resistant strains. Children infected with macrolide-resistant *M. pneumoniae* have a longer duration of fever after initiating macrolide therapy than those infected with a macrolide-sensitive strain, and macrolide was more likely to change to another antimicrobial [8]. However, in the study by Suzuki *et al.* [8], patients infected with macrolide-resistant strains were more likely to receive erythromycin or clarithromycin than azithromycin. No cohort studies have been performed in an adult population. A previous case report described a 28-yr-old lady with CAP, who had persistent symptoms after clarithromycin therapy, and later responded to intravenous pazufloxacin [9]. The strain was found to carry the A-to-G transition at position 2,063. For our patient, despite 9 days of azithromycin therapy, there was persistent fever and radiological progression of consolidation. However, after initiation of tigecycline, fever subsided within 24 h, and there was rapid resolution of pulmonary infiltrates. As the patient travelled to mainland China shortly before the onset of symptoms, where she has had contact with her father with respiratory symptoms, it is possible that she could have acquired the resistant organism from Xi'an. There has not been any published data on macrolide-resistant *M. pneumoniae* in this city, but a high prevalence of macrolide resistance has been found in Shanghai, China [5].

The optimal treatment for a serious infection caused by macrolide-resistant *M. pneumoniae* remains uncertain. Pharmacokinetics and *in vitro* data indicate that tetracyclines and fluoquinolones are potential options. For macrolide-resistant strains with the A2063G mutation, the MIC was

0.0625–1 µg·mL^{-1} for minocycline and 0.0625–0.125 µg·mL^{-1} for moxifloxacin [4]. Tigecycline, a glycylcyline, has a more favourable pharmacokinetic and pharmacodynamic profile than the tetracyclines. The MIC of tigecycline (ranging 0.125–0.5 µg·mL^{-1}) against *M. pneumoniae* is lower than that of tetracycline (0.5–4 µg·mL^{-1}) and is similar to minocycline (0.06–0.5 µg·mL^{-1}) [10]. However, further clinical trials would be required to determine whether this translates to clinical superiority. Since both tetracyclines and fluoroquinolones are contraindicated in children, management of serious infection caused by macrolide-resistant *M. pneumoniae* would be challenging.

In this report, we have provided evidence that a transition from A-to-G at position 2,063 position to be associated with treatment failure. We propose that other antibiotics active against *M. pneumoniae*, such as tetracyclines or fluoroquinolones, should be used if a patient has clinical failure after macrolide therapy. Local surveillance would be important to determine the prevalence of macrolide resistance among *M. pneumoniae*, and will provide important information regarding empirical therapy against *M. pneumoniae*.

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