### Case report

A 6-year-old Chinese boy presented to the Department of Paediatrics and Adolescent Medicine of Tuen Mun Hospital in Hong Kong in May 2010 with fever and non-productive cough for 3 days. He enjoyed good past health and his routine immunisations had been up to date. Physical examination revealed bilateral non-suppurative conjunctivitis and multiple small cervical lymph nodes. Chest examination yielded right lower zone crackles. The oxygen saturation was 96% on room air. The chest X-ray (CXR) on admission showed consolidation of the right lower lobe. Initial blood tests revealed a normal peripheral white blood cell count (WBC) of 5.3 x 10⁹/L (reference range, 4.5-11.0 x 10⁹/L), a mildly elevated alanine transaminase (ALT) level of 42 U/L (reference range, 5-25 U/L), and elevated C-reactive protein level of 133 mg/L (reference level, <5 mg/L). The patient was treated as a community-acquired pneumonia (CAP) with cefotaxime and oral clarithromycin. The fever and respiratory symptoms persisted and vancomycin was added on the second day of admission. By the third day of hospitalisation, he developed a generalised erythematous maculopapular and blanchable but non-pruritic skin rash, initially over the trunk (Fig), and later that day it spread to the face and limbs. There were no mucosal or target lesions. Nor was there any history of animal or bird contact, or recent travel out of Hong Kong.

The patient’s condition deteriorated that day; there being gradual oxygen desaturation (93% saturation on 1L-minute oxygen supplementation). A repeated CXR showed a newly developed right pleural effusion, but the WBC was within normal limits. The ALT was 61 U/L, while the creatinine kinase and lactate dehydrogenase levels were elevated (1301 U/L and 2055 U/L, respectively). In view of the deteriorating clinical condition, the antibiotic regimen was switched to meropenem and azithromycin. Culture from respiratory tract specimens only grew oral commensals, whilst two sets of blood culture incubated for 5 days grew no organisms. Urine for Legionella antigen (BinaxNOW, Binax), nasopharyngeal aspirate (NPA) for influenza A and B rapid antigen detection (BD Directigen EZ Flu A+B, Becton Dickinson), gastric lavage examined by polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* were all negative. Examination of NPA specimens by PCR for atypical pneumonia were negative for *Legionella pneumophila*, *Chlamydophila pneumoniae*, and *Bordetella pertussis*. The *Mycoplasma pneumoniae* PCR was positive with a cycle threshold value of 24.0. The cold agglutinin titre was 32 (not elevated).

The pleural effusion was drained by image-guided insertion of a pigtail-catheter. *Mycoplasma pneumoniae* PCR was also performed on the pleural fluid specimen, but the result was negative. In the fifth day of hospitalisation, the patient was started on oral doxycycline 50 mg (2 mg/kg) twice daily. The fever resolved by the next day, and subsequent CXRs showed gradual resolution of the consolidation. He completed 10 days of oral doxycycline and was discharged after 17 days of hospitalisation. Serology on paired samples collected 2 weeks apart (days 2 and 15 of hospitalisation) showed that using the particulate agglutination test (SERODIA-MYCOII; Fujirebio Inc, Tokyo, Japan), the *Mycoplasma pneumoniae* PCR was positive with a cycle threshold value of 24.0. The cold agglutinin titre was 32 (not elevated).

### Key words

Community-acquired infections; Doxycycline; Drug resistance, bacterial; Macrolides; *Mycoplasma pneumoniae*
肺炎黴漿菌（Mycoplasma pneumoniae）是引致兒童非典型肺炎最常見的病原之一。長久以來，當β-lactams對社區型肺炎患者無效時，我們都會改為處方大環內酯類抗生素（macrolides）。本文報告首宗對大環內酯類抗生素呈耐藥性的肺炎黴漿菌而引致嚴重社區型肺炎的本地病例，其23S核蛋白體RNA基因上的2063位發生了A→G點突變。此外，我們在十宗肺部感染個案中，利用聚合酶鏈反應確認了額外兩株對大環內酯類抗生素呈耐藥性的肺炎黴漿菌耐藥株。所以，最終有三分之一的病例（即十宗病例中有三宗）是對大環內酯類抗生素呈耐藥性的肺炎黴漿菌所引致的。

一名六歲男孩因感染對大環內酯類抗生素呈耐藥性的肺炎黴漿菌而引致嚴重社區型肺炎

pneumoniae titre rose from 1:40 to 1:10 240. The DNA extract prepared from clinical specimen was analysed by sequencing the domain V of the 23s rRNA gene,1 which showed an A-to-G transition at position 2063 of the 23S rRNA gene. This mutation indicates a high level of macrolide resistance.1

**Discussion**

Macrolide binds to the central loop in domain V of 23s rRNA. This results in blockage of the path of the elongating peptidyl chain through the ribosome due to steric hindrance, leading to inhibition in protein synthesis. A mutation in the sequence of the central loop of domain V of 23s rRNA gene therefore appears to confer resistance to macrolides.2

Macrolide-resistant M pneumoniae was first described among children with CAP in Japan in 2000,3 and the first adult case in 2007.3 Since the recognition of this phenomenon in 2000, there has been rapid rise in the number of such cases in Japan.3 Macrolide-resistant M pneumoniae has also been described in China where its prevalence was believed to be very high. In Shanghai, 53 isolates from paediatric patients with respiratory tract infections were analysed, of which 44 (83%) were resistant to macrolides (83%) and all manifested the A-to-G transition mutation at position 2063 in the 23s rRNA gene.4 In one series from Beijing, 92% of the M pneumoniae isolated from children with respiratory tract infections were resistant to macrolides.5

*Mycoplasma pneumoniae* is endemic in Hong Kong, and as in other large urban areas, epidemics occur once every 3 to 5 years.2 Hong Kong has endured an upsurge of cases of *M pneumoniae* infection since May 2010.6 During the period March 2010 to August 2010, we have analysed 10 respiratory tract samples from patients with CAP that were positive for *M pneumoniae* by PCR; three had a point mutation of 23S rRNA at position A-to-G at position 2063 (Table). The first case of macrolide-resistant *M pneumoniae* in Hong Kong was reported earlier this year,7 in a 24-year-old woman with travel history to Xi’an. None of our patients with macrolide-resistant *M pneumoniae* had a travel history or recent contact with sick patients from China. This implies that in Hong Kong, macrolide-resistant *M pneumoniae* might be spreading around unnoticed.

In a study analysing 13 strains of macrolide-resistant *M pneumoniae* in Japan, 10 (77%) of the strains possessed an A-to-G transition at position 2063. Other mutations included: A-to-C transversion.

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**FIG. Generalised erythematous maculopapular blanchable non-pruritic skin rash seen over the trunk region**

**TABLE. Patient information**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Date</th>
<th>Mutation in 23s rRNA</th>
<th>Treatment</th>
<th>Travel history</th>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>M</td>
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<td>A2063G</td>
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<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
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<td>A2063G</td>
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</tr>
<tr>
<td>3</td>
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<td>A2063G</td>
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</tr>
<tr>
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<tr>
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<tr>
<td>6</td>
<td>10</td>
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<tr>
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<tr>
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<td>F</td>
<td>8/2010</td>
<td>Absent</td>
<td>Doxycycline</td>
<td>Yes (Korea)</td>
</tr>
</tbody>
</table>
at position 2063, A-to-G transition at position 2064 and C-to-G transversion at position 2067. Strains possessing a mutation A-to-G transition at position 2063 showed very high levels of macrolide resistance (erythromycin, minimum inhibitory concentration [MIC] ≥256 μg). The majority of the strains isolated in Shanghai and Beijing also bore the same point mutation in the 23s rRNA gene.1,4

Clinically, infections caused by macrolide-resistant as opposed to sensitive strains of *M pneumoniae* were characterised by a prolonged duration of fever (4±2 days vs 2±1 days, *P*<0.01) and persistent cough (11 days vs 7 days).3 However, most of the patients received macrolide treatment despite being infected with macrolide-resistant strains. In our patient, the fever actually responded immediately after initiation of doxycycline. Macrolide-resistant strains of *M pneumoniae* were not shown to cause exceptionally severe illness.

Upper respiratory tract infections caused by *M pneumoniae* are usually self-limiting and no treatment is required. Lower respiratory tract infections also tend to resolve spontaneously without treatment, depending on their severity. In a meta-analysis by Mills et al,8 there was no improvement in clinical outcome by adding agents active against atypical agents in non-severe CAP, except for patients with *Legionella* infections. However, in severe cases of *M pneumoniae*, antibiotics can shorten the duration of infection.2 There is no clinical study to date to evaluate the optimal treatment regimen for macrolide-resistant *M pneumoniae*. Laboratory data from Japan have demonstrated favourable MIC with levofloxacin and doxycycline.9 Twelve strains of macrolide-resistant *Mycoplasma* were analysed in this study, of which 10 possessed the A2063G of macrolide-resistant strains. In our patient, the fever actually responded immediately after initiation of doxycycline. Macrolide-resistant strains of *M pneumoniae* were not shown to cause exceptionally severe illness.

The use of tetracyclines is limited to children older than 8 years due to their liability to cause permanent dental discolouration.10 Since the colour degradation products of tetracycline may be deposited in the dentine and incorporated diffusely in the enamel, the period between odontogenesis and the completion of enamel formation in permanent teeth is the critical interval when tetracyclines should be avoided. As enamel formation is usually completed by the age of 8 years, these antimicrobials can generally be used without concern for dental staining. Dental staining also depends on the duration and dosage of tetracycline. Doxycycline has a lower risk of dental staining, and since the duration of courses is relatively short, it was a drug of choice in this case. Fluoroquinolones are not recommended for use in children younger than 18 years of age, due to their potential for damaging cartilage, as demonstrated in animal models.19 However, growing experience has demonstrated that their usage in children is actually well tolerated and that they do not appear to cause significant arthropathy.19

We have presented the first locally acquired case of severe CAP in a child caused by macrolide-resistant *M pneumoniae* with an A-to-G mutation at position 2063 in the 23s rRNA gene. We have also identified two other local cases of macrolide-resistant *M pneumoniae* infection. Macrolides are still considered the first-line therapy for CAP not responding to beta-lactams in children. However, with the emergence of macrolide-resistant *M pneumoniae* strains, alternative antibiotic choices including tetracyclines and fluoroquinolones should be considered in children experiencing treatment failure.

References