

Caso
clinico

Case
report

Resolution of migratory pulmonary infiltrates by moxifloxacin in a patient with dual infection of *Mycoplasma pneumoniae* and *Bordetella pertussis*

Risoluzione di infiltrati polmonari migranti in un paziente con infezione da *Mycoplasma pneumoniae* e *Bordetella pertussis* a seguito di terapia con moxifloxacin

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INTRODUCTION

M*ycoplasma pneumoniae* is often isolated from patients with prolonged coughing and symptoms of atypical pneumonia [1]. If the organism is identified as the sole etiologic agent, the respiratory symptoms are usually not severe and may respond well to susceptible antibiotic treatment [2]. However, due to its ability to alter the local respiratory immunity of the hosts, infection with *M. pneumoniae* is often accompanied by that of other respiratory pathogens, such as respiratory syncytial viruses and *Streptococcus pyogenes* [3-5]. *Bordetella pertussis* is one of such respiratory pathogens that causes severe respiratory symptoms in children [6]. According to a recent report, dual infection with *M. pneumoniae* and *B. pertussis* in unvaccinated infants resulted in serious respiratory complications with fatal outcomes [7]. By contrast, the symptoms caused by *B. pertussis* infection are usually milder in adults due to the partial immunity from previous infection or immunization [8]. Thus, the

dual infection of this pathogen has often been dismissed in adult patients with *M. pneumoniae* infection. In Japan, however, because of the deaths of two infants caused by pertussis vaccine injection in 1975, the vaccination was temporarily suspended for several years [9, 10]. As a result, some people in their mid-30s these days have not yet been vaccinated against *B. pertussis*. Here, we experienced an unvaccinated Japanese woman who developed a dual infection of *M. pneumoniae* and *B. pertussis*, presenting migratory pulmonary infiltrates in chest radiographs. In this case, an increased immunological response triggered by the organisms was likely to be involved in the pathogenesis. In such a case, moxifloxacin, one of the quinolone derivatives, was more useful than macrolides or tetracyclines for the resolution of the prolonged symptoms and signs. The immunomodulatory property of moxifloxacin was thought to repress the increased lymphocyte activity, and thus facilitated a complete remission of the disease.

CASE REPORT

A 37-year-old Japanese woman came to our outpatient clinic because of a nocturnal fever and

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persistent dry cough for the previous 2 weeks. Five days prior to her visit, she was prescribed oral azithromycin (500 mg/day) for 3 days in a nearby clinic, although her symptoms did not improve (Figure 1). On physical examination, the patient looked tired. Her body temperature was 37.6°C, blood pressure was 118/74 mmHg, and pulse rate was 74 beats/min. She weighed 50 kg and was 160 cm tall. Her oral mucosa was moist and the pharynx was slightly swollen but without exudates. On examination of the neck, bilateral posterior cervical lymphadenopathy was present. No crackles or wheezes were heard on lung auscultation. Laboratory data showed an increased peripheral white blood cell count (9,400/ l) and a slightly elevated C-reactive protein level (0.67 mg/dl). Electrolytes and liver enzymes were normal. Serological assays revealed no significant elevations in antibodies to *Chlamydophila pneumoniae*, *Legionella pneumophila* and influenza virus. However, immunoglobulin M (IgM) antibody specific to *M. pneumoniae*, determined by particle agglutination, was high

(1:320) with a significant rise in the IgG titer, indicating a recent infection with the organism. Since she has not been vaccinated against *B. pertussis* in her childhood, and since the anti-pertussis toxin IgG was positive with a high agglutinin titer against Tohama strain (1:320), a diagnosis of *B. pertussis* infection was also made, indicating a dual infection with *M. pneumoniae*. A chest radiograph showed poorly-defined nodular opacities in the lingula area of the left lung (Figure 2A). Because azithromycin had not previously been effective for her symptoms, oral administration of minocycline (200 mg/day) was alternatively started immediately after the diagnosis (Figure 1). In spite of the treatment with the drug for 10 days, the symptoms persisted and the systemic inflammatory findings remained high (Figure 1). In a chest radiograph (Figure 2Ba), although the infiltrates in the left lung had improved, another patchy area of consolidation emerged in the right lower lobe indicating spatial recurrence of the infiltrates. A computed tomography (CT) image also demon-

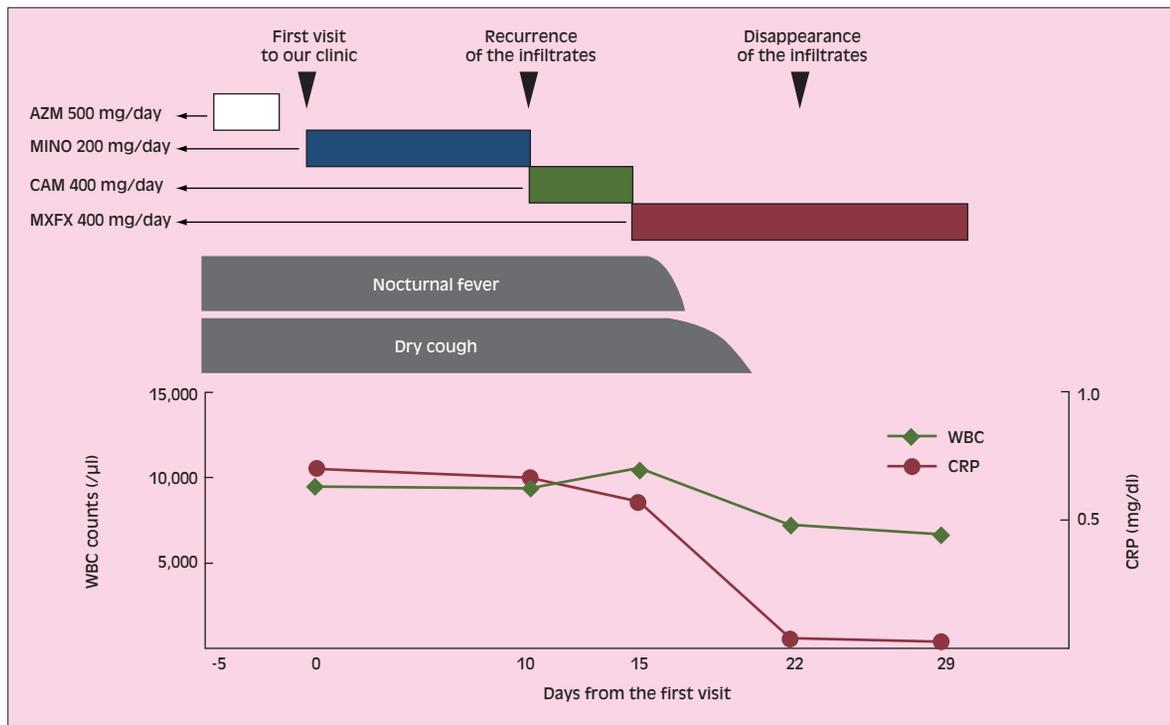


Figure 1 - Clinical course and the changes in white blood cell count in the peripheral blood (WBC), C-reactive protein level (CRP). Despite the use of azithromycin (AZM), minocycline (MINO) and clarithromycin (CAM), the patient's symptoms, such as a nocturnal fever and dry cough, continued and the systemic inflammatory findings did not improve. However, moxifloxacin (MXFX) dramatically resolved the symptoms shortly after the administration, and there were no further signs of recurrence with the continuous administration of the drug. AZM, azithromycin; MINO, minocycline; CAM, clarithromycin; MXFX, moxifloxacin; WBC, white blood cell count in the peripheral blood; CRP, C-reactive protein.

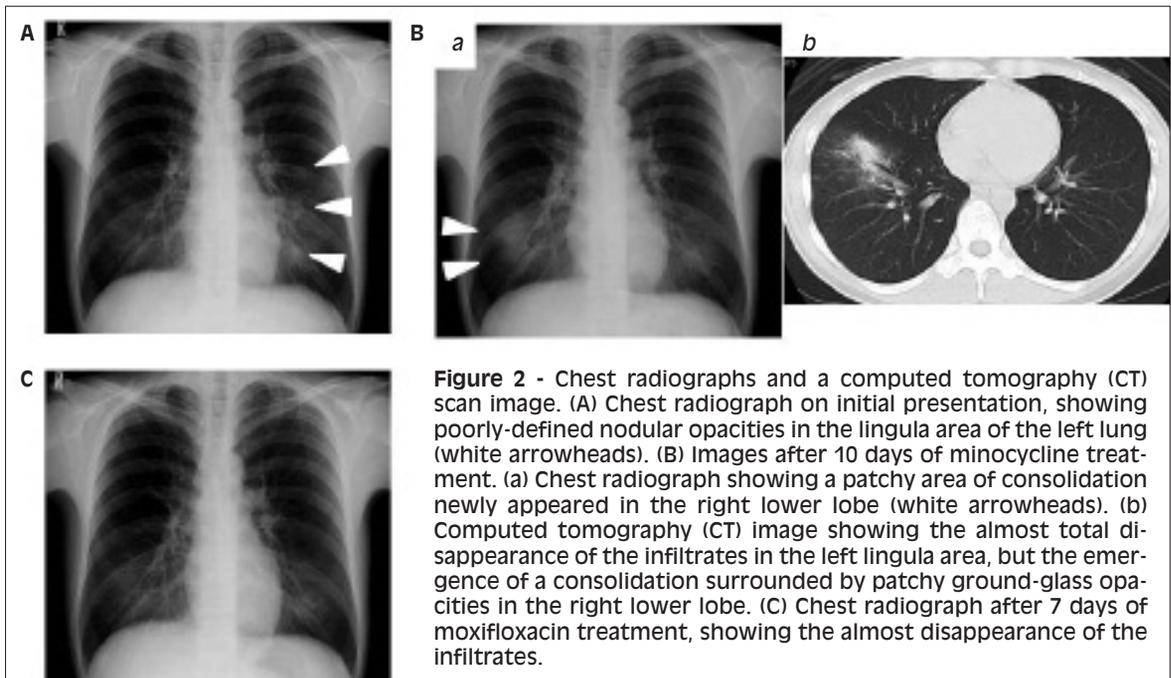


Figure 2 - Chest radiographs and a computed tomography (CT) scan image. (A) Chest radiograph on initial presentation, showing poorly-defined nodular opacities in the lingula area of the left lung (white arrowheads). (B) Images after 10 days of minocycline treatment. (a) Chest radiograph showing a patchy area of consolidation newly appeared in the right lower lobe (white arrowheads). (b) Computed tomography (CT) image showing the almost total disappearance of the infiltrates in the left lingula area, but the emergence of a consolidation surrounded by patchy ground-glass opacities in the right lower lobe. (C) Chest radiograph after 7 days of moxifloxacin treatment, showing the almost disappearance of the infiltrates.

strated the almost total disappearance of the infiltrates in the left lingula area (Figure 2Bb), but the emergence of a consolidation surrounded by patchy ground-glass opacities in the right lower lobe, presenting radiological features similar to those of organizing pneumonia [11, 12]. Since additional treatment with clarithromycin (400 mg/day) failed to improve her clinical features (Figure 1), oral administration of moxifloxacin (400 mg/day) was alternatively started. Shortly after the initiation of the drug, her prolonged symptoms, such as a nocturnal fever and dry cough, had dramatically resolved (Figure 1). After 7 days of treatment with the drug, the pulmonary infiltrates had almost disappeared (Figure 2C) and the systemic inflammatory findings had improved (Figure 1). Moxifloxacin was continued for the next 7 days (total 2 weeks), and no recurrence of the symptoms or the pulmonary infiltrates was noted afterwards, indicating a complete remission of the disease.

DISCUSSION

Since mycoplasmas are known to stimulate the activity and cytokine production of lymphocytes, the symptoms caused by the organisms are believed to be immune-mediated rather than induced directly by their cellular toxicity [13, 14]. Therefore, infection with *M. pneumoniae*

ae has often been associated with the subsequent onset of organizing pneumonia, an immune-mediated lung disease histopathologically characterized by intraalveolar granulation and the infiltrate of mononuclear inflammatory cells [11, 15, 16]. In our case, due to the lack of histological evidence, organizing pneumonia was not considered likely. However, the radiological features were similar to those of organizing pneumonia, such as the migratory pulmonary infiltrates and the patchy ground-glass opacities in the lower lobe, which strongly suggested the involvement of an increased immunological response in the pathogenesis of pneumonia [11, 12]. Previous studies have demonstrated that *B. pertussis* infection stimulated the activity of T-lymphocytes and increased the production of proinflammatory cytokines in both humans and experimental animals [17]. In our case, since the patient was co-infected with *M. pneumoniae* and *B. pertussis*, these organisms were thought to exert multiplicative effects that enhanced the cellular immunity of the patient.

For patients with *M. pneumoniae* or *B. pertussis* infection, the use of macrolides or tetracyclines has been the mainstay of the treatment [18, 19]. In our case, however, macrolides, such as azithromycin and clarithromycin, failed to improve the clinical features of the patient (Figure 1). Although minocycline was partially effec-

tive for the pulmonary infiltrates, it did not prevent the recurrence of other infiltrates (Figure 2B). Since the use of moxifloxacin immediately resolved the prolonged symptoms of the patient and the migratory pulmonary infiltrates without any recurrence, this drug was thought to be responsible for the complete remission of the disease. In addition to its broad-spectrum antimicrobial properties, moxifloxacin exerts immunomodulatory effects by reducing the proinflammatory cytokine production from lymphocytes [20-22]. In the present case, since the increased activity of lymphocytes was mainly involved in the pathogenesis, the immunomodulation by moxifloxacin was thought to be the mechanism responsible for the remission of the disease. Recently, we have demonstrated in basic studies that the functional inhibition of delayed rectifier K⁺-channels (Kv1.3) represses the activity of lymphocytes [23, 24]. Since the channels are highly expressed in the plasma membrane of T-lymphocytes, moxifloxacin may have exerted immunomodulatory effects through direct inhibition of the channels

[25]. In this regard, besides the use of corticosteroids, the use of selective Kv1.3-channel blockers may also be useful for the resolution of migratory pulmonary infiltrates [11, 12].

In summary, this is the first report of an adult patient with a dual infection of *M. pneumoniae* and *B. pertussis*, for which the usefulness of moxifloxacin for the resolution of prolonged symptoms and the migratory pulmonary infiltrates was demonstrated. The immunomodulatory property of moxifloxacin was thought to repress the increased lymphocyte activity and thus enabled complete remission of the disease.

Keywords: *Mycoplasma pneumoniae*, *Bordetella pertussis*, dual infection, migratory pulmonary infiltrates, immunomodulation, moxifloxacin.

Declaration of interest

The authors declare no conflicts of interest.

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SUMMARY

A 37-year-old Japanese woman, who was not vaccinated against *Bordetella pertussis*, developed a nocturnal fever with persistent dry cough for more than 2 weeks. A chest radiograph showed poorly-defined nodular opacities in the left lung. Due to the significant rise in serum antibodies for both *Mycoplasma pneumoniae* and *B. pertussis*, a diagnosis of dual infection with the organisms was made. Despite the use of susceptible antibiotics, the patient's symptoms did not improve and her chest radiograph showed migratory pulmonary infil-

trates. However, a quinolone derivative, moxifloxacin, dramatically improved her symptoms and resolved the pulmonary infiltrates shortly after administration. In this case, due to the lymphocyte-stimulatory nature of *M. pneumoniae* and *B. pertussis*, an increased immunological response was likely to be involved in the pathogenesis of pneumonia. The immunomodulatory property of moxifloxacin was thought to repress the increased lymphocyte activity, and thus facilitated complete remission of the disease.

RIASSUNTO

Una donna giapponese di 37 anni, non vaccinata per *Bordetella pertussis*, sviluppava febbre notturna, con tosse secca persistente, da oltre 2 settimane. Una radiografia del torace evidenziava la presenza di opacità nodulari scarsamente definite nel polmone sinistro.

In considerazione di un significativo innalzamento degli anticorpi sierici per *Mycoplasma pneumoniae* e *B. pertussis*, veniva posta diagnosi di doppia infezione da *M. pneumoniae* e *B. pertussis*. Nonostante l'istituzione di una terapia antibiotica attiva nei confronti di tali microrganismi, la sintomatologia non subiva miglioramenti e una nuova radiografia toracica evidenziava in-

filtrati polmonari migranti. Tuttavia, un derivato chinolonico, moxifloxacina, determinava un sostanziale miglioramento dei sintomi e la risoluzione degli infiltrati polmonari poco dopo l'inizio della terapia. In questo caso clinico, a causa dell'attività di stimolazione linfocitaria esercitata da *M. pneumoniae* e *B. pertussis*, è probabile che nella patogenesi della polmonite fosse implicato un potenziamento della risposta immune. Si è ipotizzato che le proprietà immunomodulanti di moxifloxacina abbiano represso l'aumento dell'attività linfocitaria, favorendo dunque una completa remissione della malattia.

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