Casi clinici

Case reports

Dual infection of *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* in patients with atopic predispositions successfully treated by moxifloxacin

Infezione concomitante da Mycoplasma pneumoniae *e* Chlamydophila pneumoniae *in pazienti con predisposizioni atopiche trattati con successo con moxifloxacina*

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INTRODUCTION

Acute bronchitis, a lower respiratory tract infection that causes reversible bronchial inflammation, is one of the most frequently encountered conditions in clinical practice [1]. Although more than 90% of cases are caused by viral infections, bacterial organisms, such as *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Bordetella pertussis*, are also major pathogens, particularly in young adults who were previously healthy [2]. If the organisms are identified as the sole aetiological agent, the respiratory symptoms are usually not severe and may respond well to susceptible antibiotic treatment [3-5]. However, once they are co-infected with each other, the symptoms are often prolonged and the infection sometimes causes serious respiratory complications with fatal outcomes [6-8]. Previously, we reported a case of pneumonia caused by a dual infection of *Mycoplasma pneumoniae* and *Bordetella pertussis* [9]. In this case, due to the migratory feature of pulmonary infiltrates, an increased immunological response was likely to be involved in the pathogenesis. According to recent studies, infection with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* both triggers the onset of bronchial asthma and exacerbates its wheezing-related symptoms [6, 10]. Although the mechanisms are not fully understood, these organisms are thought to stimulate pro-inflammatory cytokine production, which aggravates the allergic status and induces airway hypersensitivity [11]. Since the activity of lymphocytes depends on their cytokine productivity, dual infection of the organisms would additively enhance the cellular immunity, which may contribute to the prolongation of the symptoms and the severity of the disease [12]. Here, we experienced two cases of dual infection with *Mycoplasma pneumoniae* and *Chlamydophila pneumonia* complicated by atopic dermatitis or allergic rhinitis. In these cases, due to the atopic predisposition of the patients, an immunological response was easily triggered by the infectious stimuli, and enhanced immunity was likely involved in the pathogenesis. In these cases, moxifloxacin, one of the quinolone derivatives, was more useful than macrolides or tetracycline for resolving the prolonged symptoms. The immunomodulatory property of moxifloxacin was thought to repress the increased lymphocyte activity, and

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thus facilitated complete remission of the disease.

CASE REPORT

Case 1

A 24-year-old woman with atopic dermatitis noticed her atopic eczema worsening despite the use of topical corticosteroids. Three days later, she developed a nocturnal fever and productive cough which persisted for two weeks. Since the use of analgesics and antitussives did not improve her symptoms, she came to our outpatient clinic.

On physical examination, the patient appeared exhausted. Her body temperature was 37.1°C, blood pressure was 112/72 mmHg, and pulse rate was 74 beats/min. She weighed 55 kg and was 168 cm tall. She had an intensely itchy, dry rash on her face and whole body, indicating generalized atopic eczema. Her oral mucosa was moist and the pharynx was slightly swollen.

On examination of the neck, cervical lymph nodes or masses were not palpable. No crackles, wheezes or stridors were heard on lung auscultation. Laboratory data showed a normal peripheral white blood cell count (4,500/μl), but a slightly elevated C-reactive protein level (0.18 mg/dl). Although electrolytes and liver enzymes were normal, the serum immunoglobulin E (IgE) level was markedly elevated (5000 IU/ml), indicating an exacerbation of the atopic dermatitis [13].

Serological assays revealed no significant elevations in antibodies to *Bordetella pertussis* or influenza virus. However, the IgM antibody spe-

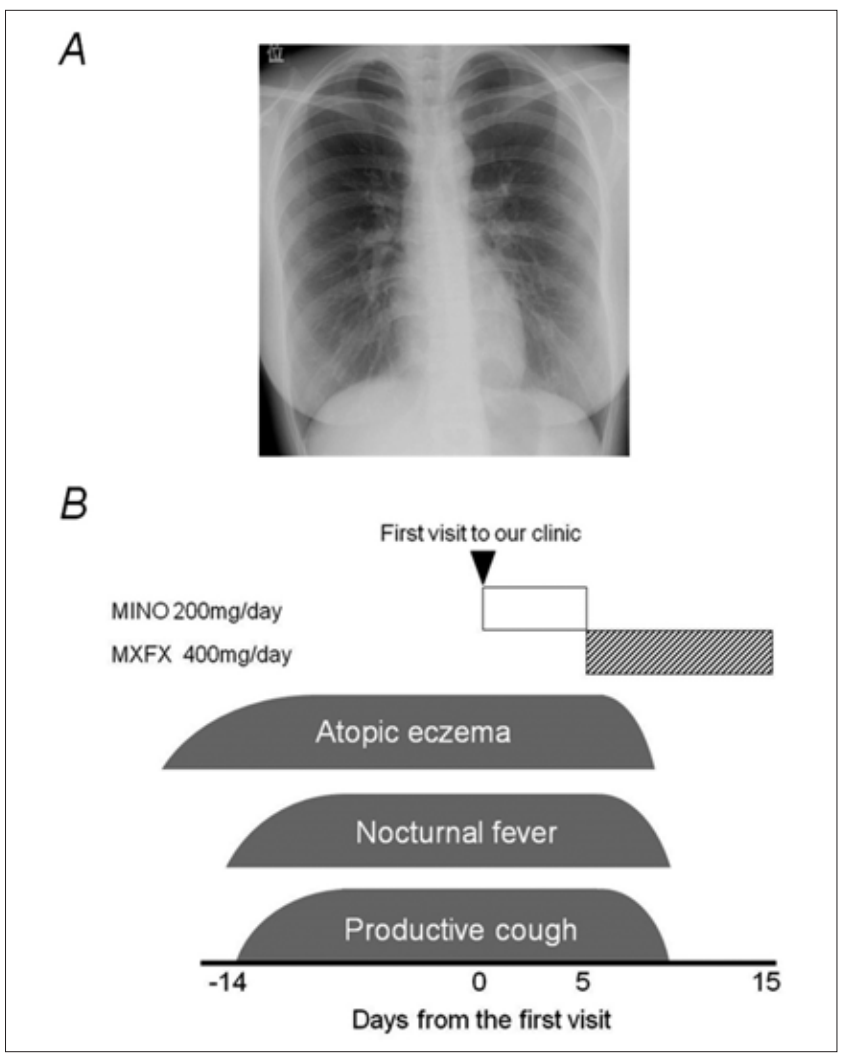

Figure 1 - Chest radiograph (A) and clinical course (B) of Case 1. (A) A chest radiograph of the patient on initial presentation shows no signs of pulmonary infiltrates or consolidation. (B) Following the worsening of atopic eczema, the patient developed a nocturnal fever and productive cough which persisted for two weeks. Despite the use of minocycline (MINO), her symptoms continued. However, moxifloxacin (MXFX) dramatically resolved the symptoms and improved her atopic eczema shortly after the administration. There were no further signs of recurrence with the continuous administration of the drug. MINO, minocycline; MXFX, moxifloxacin.

cific to *Mycoplasma 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 the IgM antibody to *Chlamydophila pneumoniae*, determined by enzyme-linked immunosorbent assay (ELISA), was also positive, with a significant rise in the cut-off index (3.656) [14], a diagnosis of a dual infection with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* was made. Because a chest radiograph revealed no signs of pulmonary infiltrates or consolidation (Figure 1A), the patient was not likely to have pneumonia. Therefore, acute bronchitis due to the organisms was considered to be the cause of her symptoms. Since oral administration of minocycline (200 mg/day) for five days failed to improve her symptoms (Figure 1B), the 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 productive cough, had completely resolved, together with a dramatic improvement of the atopic eczema (Fig. 1B). Moxifloxacin was continued for 10 days, and no recurrence of the symptoms or signs was noted afterwards, indicating complete remission of the disease.

Case 2

A 16-year-old boy with a past history of allergic rhinitis developed rhinorrhea with nasal itching and sneezing, followed by a nocturnal fever and persistent dry cough for three weeks. Since the symptoms did not improve despite the use of antihistamines, he came to our outpatient clinic.

On physical examination, the patient looked

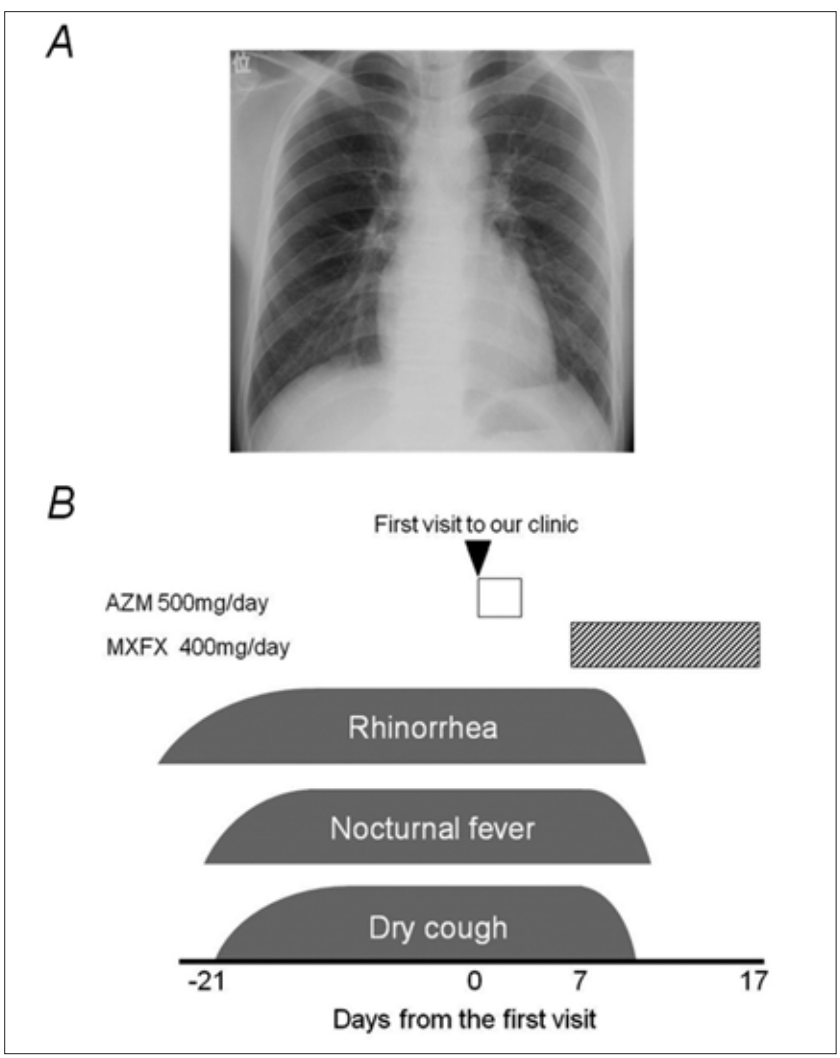

Figure 2 - Chest radiograph (A) and clinical course (B) of Case 2. (A) A chest radiograph of the patient on initial presentation shows no signs of pulmonary infiltrates or consolidation. (B) Following the recurrence of allergic rhinitis with rhinorrhea, the patient developed a nocturnal fever and dry cough which persisted for three weeks. Despite the use of azithromycin (AZM), his symptoms 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; MXFX, moxifloxacin.

tired. His body temperature was 37.0°C, blood pressure was 122/68 mmHg, and pulse rate was 66 beats/min. He weighed 60 kg and was 178 cm tall. Although his oral mucosa was moist and the pharynx was slightly reddish, there were no signs of postnasal drip or posterior pharynx cobblestoning.

On examination of the neck, bilateral posterior cervical lymphadenopathy was present. No crackles, wheezes or stridors were heard on lung auscultation.

Laboratory data showed a normal peripheral white blood cell count (5,700/ ml). Liver enzymes and C-reactive protein levels were not elevated. Due to the significant rise in IgM antibodies to both *Mycoplasma pneumoniae* (1:320) and *Chlamydophila pneumoniae* (Index 1.618), the diagnosis of a dual infection with the organisms was made.

Since symptoms suggestive of postnasal drip syndrome or gastroesophageal reflux disease were absent, and since a chest radiograph revealed no signs of pulmonary infiltrates (Figure 2A), acute bronchitis caused by the organisms was likely responsible for the prolonged coughing and fever. Because oral administration of azithromycin (500 mg/day) for 3 days did not improve the symptoms (Figure 2B), the administration of moxifloxacin (400 mg/day) was alternatively started.

The prolonged symptoms, including rhinorrhea, nocturnal fever and dry cough, had dramatically resolved shortly after the initiation of the drug (Figure 2B).

DISCUSSION

Patients with atopic predispositions are prone to develop autoimmune diseases due to the hypersensitivity of T-helper 2 lymphocytes or the dysregulated activity of B-lymphocytes [15-17]. In our cases, since both patients were predisposed to atopic disorders, such as atopic dermatitis and allergic rhinitis, the lymphocytes were thought to be easily activated by infectious stimuli, as previously demonstrated in atopic children [11].

Mycoplasmas are known to stimulate the activity and cytokine production of lymphocytes, and the symptoms caused by the organisms are believed to be immune-mediated rather than induced directly by their cellular toxicity [18, 19]. Therefore, infection with *Mycoplasma pneumoniae* has often been associated with the subsequent onset of immune-mediated systemic disorders, such as Stevens-Johnson syndrome, thrombocytopenic purpura and organizing pneumonia [20-22].

In our cases, although the patients were not complicated with such disorders, the exacerbation of atopic dermatitis or allergic rhinitis before the onset of acute bronchitis strongly suggested the involvement of an increased immunological response in the pathogenesis. Previous studies have demonstrated in both *in vitro* and *in vivo* experiments that *Chlamydophila pneumoniae* infection also stimulates the activity of leukocytes, and thus increases the production of proinflammatory cytokines [23, 24]. In our cases, since the patient was co-infected with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, these organisms were thought to exert multipliable effects that enhanced the cellular immunity of the patients.

For patients with *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* infection, the use of macrolides or tetracycline has been the mainstay of the treatment [3, 4]. In our cases, however, azithromycin and minocycline failed to improve the clinical features of the patients (Figures 1B and 2B). Since the use of moxifloxacin immediately resolved the prolonged symptoms in both patients 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, which reduces the production of pro-inflammatory cytokines from lymphocytes, exerts more pronounced immunomodulatory effects than the other antibiotics [25-27]. In our cases, 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.

Previously, we demonstrated in basic studies that the functional inhibition of delayed rectifier K^+-channels (Kv1.3) represses the activity of lymphocytes [28, 29].

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 [12]. Recently, we demonstrated in two cases that non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit the Kv1.3-channels in lymphocytes, actually suppressed the increased immunological response in patients with atopic predispositions [29, 30].

In this regard, besides the use of moxifloxacin, the use of selective Kv1.3-channel blockers or NSAIDs may also have been beneficial in our cases.

In summary, this is the first report of dual infection with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* in patients with atopic predispositions, for which the usefulness of moxifloxacin for the quick resolution of the symptoms 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, Chlamydophila pneumoniae, dual infection, atopic predispositions, enhanced immunity, moxifloxacin.

Declaration of interest

The authors declare no conflicts of interest.

Authors' contributions

IK analysed and interpreted the patients' data. Both authors approved the final manuscript.

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SUMMARY

We report two cases of dual infection with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* complicated by atopic dermatitis or allergic rhinitis. After exacerbations of atopic eczema or rhinitis, both patients presented a nocturnal fever with persistent cough for more than two weeks. Although the use of susceptible antibiotics, such as minocycline or azithromycin, failed to work, moxifloxacin completely resolved their prolonged symptoms shortly after the administration together with a dramatic improvement of the atopic symptoms. Since the patients in question were predisposed to atopic disorders and their lymphocytes were hypersensitive, an immunological response was thought to be easily triggered by the organisms. Additionally, due to the lymphocyte-stimulatory nature of *M. pneumoniae* and *C. pneumoniae*, enhanced immunity was likely to be involved in the pathogenesis. The immunomodulatory property of moxifloxacin was thought to repress the increased lymphocyte activity, and thus facilitated complete remission of the disease.

RIASSUNTO

Gli autori riportano due casi di infezione concomitante da Mycoplasma pneumoniae *e* Chlamydophila pneumoniae *complicate da dermatite atopica o rinite allergica. In seguito a riacutizzazioni dell'una o dell'altra patologia, entrambi i pazienti presentavano febbre notturna con tosse persistente per oltre due settimane. Dopo l'iniziale fallimento di una terapia antibiotica a base di minociclina o azitromicina, il trattamento con moxifloxacina ha determinato la completa risoluzione della prolungata sintomatologia già dopo breve tempo dalla somministrazione, insieme a un sostanziale miglioramento dei sintomi atopici. In questi casi, poiché i pazienti presentavano una predisposizione per i disturbi atopici e una ipersensibilità linfocitaria, si è ritenuto che i microrganismi abbiano potuto facilmente scatenare una risposta immunologica. Inoltre, considerata l'attività di stimolazione che* M. pneumoniae *e* C. pneumoniae *esercitano sui linfociti, è probabile che nella patogenesi fosse coinvolto un potenziamento dell'immunità. Si è ipotizzato che le proprietà immunomodulanti di moxifloxacina abbiano represso l'aumentata attività linfocitaria, facilitando quindi la remissione completa della malattia.*

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