Acute Bronchitis Caused by *Bordetella Pertussis* Possibly Co-Infected with *Mycoplasma Pneumoniae*

**Patient:** Female, 49

**Final Diagnosis:** Acute bronchitis caused by *Bordetella pertussis*

**Symptoms:** Persistent productive cough

**Medication:** —

**Clinical Procedure:** Antibiotics treatment

**Specialty:** Infectious Diseases

**Objective:** Rare co-existence of disease or pathology

**Background:** *Mycoplasma pneumoniae* and *Bordetella pertussis* are among the causative pathogens of human acute bronchitis, which usually has mild symptoms. However, if there is a co-infection, the symptoms often can be prolonged and occasionally can lead to severe respiratory complications.

**Case Report:** A 49-year-old Japanese female, who had not been vaccinated for *B. pertussis*, developed a persistent productive cough which became vigorous, and occasionally caused difficulty breathing and vomiting. Since serum IgM to *M. pneumoniae* was positive and IgG to *B. pertussis* was significantly elevated, and there were no findings of pneumonia on a chest x-ray film, we made a diagnosis of acute bronchitis caused by *B. pertussis* with possible co-infection with *M. pneumoniae*. The use of garenoxacin, a quinolone derivative, failed to work; however, a macrolide antibiotic clarithromycin dramatically improved her symptoms shortly after its administration.

**Conclusions:** In this patient case, because of the lymphocyte-stimulatory nature of *M. pneumoniae* and *B. pertussis*, an increased immunological response was likely to be involved in the pathogenesis of the symptoms. The immunosuppressive effect of clarithromycin was considered to repress the increased lymphocyte activity, facilitating the remission of the disease.

**MeSH Keywords:** *Bordetella Pertussis* • Clarithromycin • Coinfection • *Mycoplasma Pneumoniae*
Background

Acute bronchitis is a lower respiratory tract infection characterized by reversible bronchial inflammation. It is among the most frequently encountered conditions in daily clinical practice [1]. Although viral infections are the major cause of acute bronchitis, accounting more than 90% of cases, microorganisms such as Mycoplasma pneumoniae, Bordetella pertussis, and Chlamydophila pneumoniae are also causative pathogens, especially in younger patients who are normally healthy [2]. These organisms often cause atypical pneumonia, which is characterized by specific respiratory symptoms such as persistent dry cough. In cases where these organisms are identified as the single causative pathogen, the respiratory symptoms are usually mild and respond well to susceptible antibiotic therapy [3–5]. However, if there is a co-infection, the symptoms can often be prolonged [6] and the infection can occasionally lead to severe respiratory complications with serious outcomes [7,8]. Recently, we reported 2 cases of acute bronchitis caused by a dual infection of M. pneumoniae and C. pneumoniae, which were successfully treated by the quinolone derivative antibiotic moxifloxacin [9]. In these cases, because of the lymphocyte-stimulatory nature of the organisms [10], increased immunological responses were likely to have been involved in the pathogenesis. Here, we report a case of acute bronchitis with co-infection of M. pneumoniae and B. pertussis, for which the effectiveness of clarithromycin was demonstrated. In this case, the immunosuppressive effect of clarithromycin was considered to have repressed the increased immunological reaction by the pathogens, leading to the resolution of the symptoms.

Case Report

A 49-year-old Japanese female patient came to our outpatient clinic because of persistent productive cough of more than 3 weeks, which originally followed symptoms such as sore throat and running nose, but was not accompanied by fever. The coughing became vigorous during a single expiration, occasionally causing difficulty breathing and vomiting. The patient had no other comorbid diseases, nor had she been vaccinated for B. pertussis before, we also made a diagnosis of B. pertussis infection, revealing a dual infection with M. pneumoniae. Since symptoms suggestive of gastroesophageal reflux disease or postnasal drip syndrome were absent, and since a chest or sinus x-ray film demonstrated no findings of pneumonia (Figure 1A) or sinusitis (Figure 1B), the organisms were likely to cause acute bronchitis. Because initial together with antitussives. However, these drugs did not improve her symptoms. On physical examination, the patient appeared tired. Her body temperature was 36.6°C, blood pressure was 131/73 mmHg, and pulse rate was 84 beats/minute. She weighed 60 kg and was 161 cm tall. Although her oral mucosa was moist, and the pharynx was slightly reddish, there were no signs of posterior pharynx cobblestoning or postnasal drip. On examination of the neck, cervical lymph nodes or masses were not palpable. On lung auscultation, no cracks, wheezes or stridors were heard. Laboratory data showed a slightly increased peripheral white blood cell count (8600/mL) and a C-reactive protein level (0.07 mg/dL). However, liver enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were not elevated (AST 16 IU/L; ALT 12 IU/L). A serological assay demonstrated no significant elevation in an antibody against C. pneumoniae. On the other hand, IgM antibody specific to M. pneumoniae, determined by enzyme immunoassay (ImmunoCard Mycoplasma), was strongly positive. Previous studies have revealed the high incidence of false positive results for ImmunoCard Mycoplasma test due to the past infection with the organism [11,12]. In our case, however, the kit showed very intense blue color reached after substrate solution. According to Matas et al., such strong intensity well corresponded to the highest value of IgM antibodies in Serodia Myco II particle agglutination test, ranging from 1: 320 to 1: 2560 or greater [13]. Additionally, in the present case, the patient’s most recent infection with M. pneumoniae occurred 9 months ago. Although the IgM antibody to M. pneumoniae can remain up to a year, Ishii et al. found that the average period of its presence was 180 days, which became significantly shorter in patients without smoking, asthma, or pulmonary infiltrates in chest x-ray [14]. In our patient case, 9 months were thought to provide enough time to lower the raised IgM level into the undetectable range before the current infection. Plus, in the most current episode, the patient reported systemic symptoms that are often accompanied by M. pneumoniae infection such as nausea, headache, malaise, and joint pain. Therefore, the positive result of the IgM antibody test was thought to indicate a recent infection with the organism. However, since we did not perform polymerase chain reaction (PCR) detection from throat specimens to confirm the presence of the organism, it may still difficult to make a definite diagnosis of M. pneumoniae infection. In our patient, IgG antibodies recognizing pertussis toxin (PT-IgG) and filamentous hemagglutinin (FHA-IgG) were both markedly elevated (PT-IgG 319 EU/mL; FHA-IgG 43 EU/mL). Because she has not been vaccinated for B. pertussis before, we also made a diagnosis of B. pertussis infection, revealing a dual infection with M. pneumoniae. Since symptoms suggestive of gastroesophageal reflux disease or postnasal drip syndrome were absent, and since a chest or sinus x-ray film demonstrated no findings of pneumonia (Figure 1A) or sinusitis (Figure 1B), the organisms were likely to cause acute bronchitis. Because initial...
administration of garenoxacin (400 mg/day) for 5 days had failed to improve her symptoms (Figure 2), the macrolide antibiotic clarithromycin (400 mg/day) was alternatively initiated. Five days after the administration of the drug, her prolonged symptoms, such as a nocturnal fever and whooping cough, had dramatically resolved (Figure 2). Clarithromycin was continued for another 5 days (total 10 days) with no recurrence of the symptoms or signs afterwards, suggesting a complete resolution of the disease.

**Discussion**

In children, *B. pertussis* is among the respiratory pathogens that leads to severe respiratory symptoms [5]. In a recent case report, co-infection with *M. pneumoniae* and *B. pertussis* in non-vaccinated children caused severe respiratory complications leading to serious outcomes [7]. In contrast, *B. pertussis* infection in adults usually causes milder symptoms, because of the partial immunity acquired from previous immunization or infection [15]. Therefore, in adult patients with *M. pneumoniae* infection, the co-infection of *B. pertussis* has frequently been overlooked. In Japan, because 2 infants died from pertussis vaccine injection in 1975 [16,17], the government temporarily ceased the vaccination for years. Consequently, in these days, there are people in their mid-40s that have not yet been vaccinated against *B. pertussis*. In addition to such lack of specific immunity to the organism, our patient had a past medical history of recurrent infection with atypical pathogens, such as *M. pneumoniae* and *C. pneumoniae*. Therefore, she was also likely to be vulnerable to the *B. pertussis* infection.

In addition to acute bronchitis caused by typical or atypical bacterial pathogens, the differential diagnosis of prolonged...
coughing includes gastroesophageal reflux disease, postnasal drip syndrome, and cough variant asthma. In the present case, however, symptoms or signs suggestive of these conditions, such as heart burn, posterior pharynx cobblestoning, or persistent dry cough, were all absent. Among a variety of atypical pathogens that cause acute bronchitis or pneumonia, including *C. pneumoniae*, *Legionella spp*, *C. psittaci*, and *Coxiella burnetii* [18], it is often difficult to distinguish *M. pneumoniae* as a sole etiologic agent. However, the presence of extrapulmonary diseases that are specific to *M. pneumoniae* infection, such as hemolytic anemia, Stevens-Johnson syndrome, encephalitis, myocarditis, and otitis media [19–22], would sometimes be helpful for the differential diagnosis. In our case, although the patient’s condition was not complicated with these systemic diseases, she noticed some symptoms that are often accompanied by *M. pneumoniae* infection.

Mycoplasmas stimulate the activity of lymphocytes and facilitate their cytokine production [10]. Therefore, the symptoms caused by Mycoplasmas are considered to be mainly immune-mediated rather than caused directly by their cellular toxicity [23]. Thus, *M. pneumoniae* infection has frequently been associated with the later development of immune-mediated systemic diseases, including hemolytic anemia, thrombocytopenic purpura, or organizing pneumonia [19,20,24–26]. On the other hand, previous studies have demonstrated in both human experimental and animal models that *B. pertussis* infection also stimulates the activity of T-lymphocytes, and thus increases the pro-inflammatory cytokine production [27]. In our case, since the patient was infected with both *M. pneumoniae* and *B. pertussis*, these atypical pathogens may have brought about multiplicative effects in enhancing the cellular immunity of the patient.

In our case, because the patient’s symptoms improved shortly after the initiation of clarithromycin (Figure 1B), this drug was considered to be responsible for the remission of the disease. Recently, macrolide resistance has often been reported for *M. pneumoniae* infection, especially in patients with the recurrent organism infections [28], but less frequently for *B. pertussis* infections [29]. Therefore, in our patient’s case, concerning the therapeutic efficacy of clarithromycin, *B. pertussis* rather than *M. pneumoniae* was likely to be the organism mainly involved in the pathogenesis. Besides its broad-spectrum antimicrobial properties, macrolide antibiotics harbor immunosuppressive properties by repressing the pro-inflammatory cytokine production from lymphocytes [30]. In our patient’s case, because an increased immunological reaction was also involved in the pathogenesis, the immunosuppression by clarithromycin provided additive mechanisms to the resolution of the symptoms. In previous studies we found that clarithromycin exerts immunomodulatory effects by inhibiting delayed rectifier K+ Channels (Kv1.3) in lymphocytes [31]. In other studies, we further revealed that drugs, including statins, anti-hypertensive drugs, and nonsteroidal anti-inflammatory drugs (NSAIDs), also effectively inhibit the channel currents [32–35]. Thus, in this context, in addition to clarithromycin [23], using these drugs that inhibit the Kv1.3-channels may also be beneficial to resolve the prolonged symptoms caused by a co-infection with *M. pneumoniae* and *B. pertussis*.

Conclusions

This is a case report of an adult patient with *B. pertussis* infection possibly co-infected with *M. pneumoniae*, for which the usefulness of clarithromycin was demonstrated. The immunosuppressive effect of clarithromycin was considered to have repressed the increased immunological reaction by the pathogens, leading to the resolution of the symptoms.

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Conflicts of interest

None.

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