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Review

A novel therapeutic strategy for mycoplasma infectious diseases

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ABSTRACT

Mycoplasma Infectious Diseases (MID) are systemic illnesses that cause vasculitis and neuritis. MID not only includes pneumonia but also diseases such as asthma, arthritis, nephritis, meningitis, encephalitis, dermatitis, pancreatitis, hepatitis, and hematologic illnesses. The broader concept of MID encompasses acute to chronic phases with diverse symptoms. Therefore, it is often confusing and difficult to identify Mycoplasma-infected patients among those with incurable diseases, such as autoimmune diseases, rheumatic diseases, nervous system disorders, and hematological disorders. Regrettably, conventional diagnosis has only been available for pneumonia, although it is critical to identify MID at early stages for effective medical treatment. A cutting-edge technology has made it possible to measure the amount of specific antibodies to species-specific mycoplasma glycolipid-antigens. This new technology provides a reliable marker to follow the state of MID by monitoring antibody titer fluctuations. A novel therapeutic strategy based on new serological diagnostics is introduced in this review.

1. Introduction

It is well known that chronic and sustained infections of pathogenic microorganisms can cause chronic inflammation and fibrosis. In these cases, treatments based on immune suppressants lead to poor results because the defensive function of the immune system against the microbe is compromised. Therefore, identifying the true causes of chronic inflammatory disease is extremely important.

Recognition of the pathogeneses of autoimmune diseases and tumors has been changing. It is now recognized that some autoimmune diseases and tumors are caused by infections with microorganisms such as bacteria and viruses.

In particular, Mycoplasma Infectious Diseases (MID) require immediate recognition and should be a high order of priority. Lyme disease, Gulf War illness (GWI), autism, depression, and dementia correlate with MID. It is important to establish social recognition of their importance and cooperation in order to prevent MID [1–3].

However, because mycoplasma is the smallest of bacteria and behaves like a virus, it is critically difficult to identify in clinical practice. However, recent cutting-edge technology has made it possible to overcome this problem and establish a diagnostic system.

2. MID (Fig. 1)

2.1. Acute MID

Mycoplasma pneumoniae is a prevalent pathogen in both upper and lower respiratory tract infections in humans. It is a common cause of community-acquired pneumonia. *M. pneumoniae* infection is typically a mild illness that is most common in young adults and school-aged children. Infections can sometimes cause pneumonia, which may require treatment or hospitalization. *M. pneumoniae* is the second-most common cause of pneumonia-related hospitalization in adults with community-acquired pneumonia. An estimated 2 million cases of *M. pneumoniae* infections occur each year in the United States. However, many infections are not diagnosed, so the actual number is likely higher, and the true size of the health problem is unknown [4].

A person infected with *M. pneumoniae* harbors these bacteria in their nose, throat, windpipe, and lungs. *Mycoplasma pneumoniae* is transmitted person-to-person through airborne droplets. People with *M. pneumoniae* infections usually spread the disease by

Abbreviations: MID, Mycoplasma Infectious Diseases; ADEM, acute disseminated encephalomyelitis; GBS, Guillain–Barré syndrome; KD, Kawasaki disease; GWI, Gulf War illness; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; CFS, chronic fatigue syndrome; FMS, fibromyalgia syndrome; ME, myalgic encephalomyelitis; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; URT, upper respiratory tract.

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coughing or sneezing while in close contact with others, who then breathe in the bacteria. The common cold-like symptoms usually include sore throat, wheezing and coughing, fever, headache, coryza, myalgia, and feelings of unease; symptom intensity and duration can be limited by early treatment with antibiotics [5].

Mycoplasma genitalium and *Ureaplasma urealyticum* are established causes of urethritis and have been implicated in other urogenital conditions [6]. Mycoplasma is also recognized as causative bacteria in asthma, rheumatic diseases, and neurological disorders [5,7–9]. It is also suspected that mycoplasmas are related to atherosclerosis and tumors (including leukemia) [10,11]. The concept of Mycoplasma-caused infectious diseases has changed to include not only pneumonia but also other chronic, serious illness, termed MID. This review focuses on *M. pneumoniae* and *Mycoplasma fermentans*

2.2. Severe complications of MID

Severe complications can result in hospitalization and sometimes death. Reported complications include severe pneumonia, exacerbation of asthma, encephalitis, hemolytic anemia, renal dysfunction, gastrointestinal complaints, erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis [12].

Chronic obstructive pulmonary disease (COPD) refers to a group of diseases that cause airflow blockage and breathing-related problems. It includes emphysema, chronic bronchitis, and (in some cases) asthma. *Mycoplasma pneumoniae* has been reported as a cause of those diseases [13,14].

There has been a case report of a 9-year-old boy with mycoplasma pneumonia who developed a pulmonary infarction [15]. He first had fever and cough, followed by difficulty breathing. Cerebral infarction has also been associated with *M. pneumoniae* infection [16]. These reports show that systemic infarction can occur in MID.

2.3. MID in allergic diseases

Mycoplasma pneumoniae may play a role in the onset of asthma in predisposed children and could be a trigger for recurrent wheezing [14,17–20]. Asthma is a disease in which airway hyperresponsiveness, increased airway contraction and secretions occur as a result of allergic airway inflammation. Mycoplasma infections are well known to exacerbate asthma pathology and cause the onset of asthma itself [17].

Allergic and atopic dermatological symptoms are also associated with *M. pneumoniae* infection [20]. Eosinophilia and eosinophilic pleural effusion have also been reported [21,22].

2.4. MID as a systemic disease

Extra-pulmonary symptoms such as autoimmune responses, central nervous system complications, and dermatological disorders have been associated with *M. pneumoniae* infections in up to 25% of cases [6,23–25].

Among the most common extra-pulmonary manifestations are disorders of the central nervous system, including meningitis, meningoencephalitis, cerebellitis, polyneuropathy, and acute disseminated encephalomyelitis (ADEM). Guillain–Barré syndrome (GBS), also known as acute inflammatory demyelinating polyradiculoneuropathy, is an acute-onset, immune-mediated disorder of the peripheral nervous system [6,22–25]. Postencephalitic epilepsy is not a rare complication of *M. pneumoniae*-related encephalitis [26].

The true incidence of hearing loss in this disease may be higher than has been previously reported. Prompt diagnosis could possibly facilitate the administration of specific treatments and lead to a better prognosis [27].

2.5. MID in chronic disease

Pulmonary fibrosis is a chronic state of *M. pneumoniae* infection that has advanced from interstitial pneumonia. Although it is difficult to definitively identify the real cause of these diseases, it may cause sarcoidosis.

Sarcoidosis appeared to be caused by an immune reaction to an infection or some other trigger (e.g., an environmental antigen) that continues after the initial infection or antigen is cleared from the body. The exact cause of sarcoidosis is not known.

Differential diagnosis of pulmonary fibrosis caused by *M. pneumoniae* includes the following: tuberculosis and non-tuberculous mycobacterial infections, bacterial pneumonia, bronchopneumonia, pulmonary fungal infections, diffuse panbronchiolitis, sinobronchial syndrome, sarcoidosis, Wegener's granulomatosis, and bronchiolealveolar carcinoma.

2.6. MID in autoimmune diseases

Autoimmune hematologic phenomena frequently occur following *M. pneumoniae* infection, including the well-known cold agglutinin disease [5,28].

Mycoplasma-related disorders may also continue immunological stimuli through chronic or repetitive infections, and become triggers for the appearance of these diseases. Autoimmune disease results from a multistep process with contributions from both genetic and environmental factors [29–31].

MID includes autoimmune diseases or autoimmune-like symptoms. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder that has a broad spectrum of effects on the majority of organs. Both SLE and *M. pneumoniae* infection may manifest as erythematosus, systemic vasculitis, nephritis, polyarthritis, and polyneuritis like Guillain–Barré syndrome [30,31]. Therefore, it is often difficult to identify mycoplasma-infected patients among those with incurable diseases such as autoimmune diseases, rheumatic disease, nervous system disorders, and hematological disorders.

There are similarities between the symptoms of mixed connective tissue disease (MCTD), Stevens–Johnson syndrome, SLE, multiple sclerosis, and MID.

Stevens–Johnson syndrome after *M. pneumoniae* infection has been reported [32]. *Mycoplasma pneumoniae* may be the most common infectious cause of Stevens–Johnson syndrome [33]. *M. pneumoniae* is also an important and highly relevant cause of bullous erythema multiforme, isolated mucositis, and Stevens–Johnson syndrome in children [34]. Patients who develop symptoms consistent with these conditions should be evaluated for *M. pneumoniae* infection and closely monitored [33,34] It is now well known that Stevens–Johnson syndrome is sometimes associated with MID [35]. *M. pneumoniae* should be added to the list of causes of Stevens–Johnson syndrome in adults with pneumonia.

Reactive arthritis has been sporadically reported as being triggered by *M. pneumonia* and *M. fermentans* [36–38]. Spondyloarthropathies are a family of long-term (chronic) joint diseases. These diseases occur in children (juvenile spondyloarthropathies) and adults. They include ankylosing spondylitis, Reiter's syndrome (reactive arthritis), psoriatic arthritis, and joint problems linked to inflammatory bowel disease. Spondyloarthropathies are sometimes called spondyloarthritis.

Recently, accumulating evidence suggests that *M. fermentans* is a pathogen of rheumatoid arthritis [9,39–41]. *Mycoplasma*