REVIEW ARTICLE

MYCOPLASMA INFECTIONS IN HUMANS

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Summary

Members of the genus *Mycoplasma* are parasitic bacteria that are widespread in nature. Several *Mycoplasma* species are important causative agents of various infections of mucosal surfaces in humans, especially in the urogenital or respiratory tracts. Pathogenetic mechanisms of mycoplasmas are intensively studied.

The "gold" standard of mycoplasma detection is cultivation, which is very difficult and time-consuming. The other options for identifying mycoplasmas include direct antigen detection or molecular-biology methods, such as polymerase chain reaction, DNA-hybridization and sequencing.

Mycoplasmas are naturally resistant to beta-lactam antibiotics because of lack of cell wall. Tetracyclines or fluoroquinolones are regarded as the first choice in the treatment of mycoplasma infections. Several reports have documented resistance of mycoplasmas to macrolides worldwide.

This report summarizes our current knowledge of laboratory diagnosis and treatment of mycoplasma infections.

Key words: Mycoplasma; infections; antimicrobial susceptibility; detection

INTRODUCTION

In 1898, the first report on microorganisms without cell wall, which caused pleuropneumonia in cattle, was published [1]. These pathogens were initially called PPLO, which means Pleuro-pneumonia like organisms. In 1929, the name PPLO was changed to *Mycoplasma* due to the characteristic morphology of cells [2]. The first human mycoplasma species was isolated in 1937 by Dienes and Edsall. It was probably *Mycoplasma (M.) hominis* that was detected in an abscess of Bartholin's gland [3]. In the 1944 Eaton described an isolation of *M. pneumoniae* from the sputum of a patient with primary pneumonia [4]. In the early 1950s additional human mycoplasmas were isolated, such as *M. fermentans* and *M. salivarium*. In 1981 the first report on sexually transmitted pathogen *M. genitalium* was published and in the 1991 *M. penetrans* was isolated from patients with human immunodeficiency virus infection [5,6].

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Mycoplasmas belong to the family *Mycoplasmataceae*, order *Mycoplasmatales*, class *Mollicutes*. More than 200 *Mycoplasma* species have been identified in humans, animals, plants and arthropods so far, but only a few of these have been proven to cause diseases in humans.

Mycoplasmas are the smallest and simplest prokaryotes with a minimal reproductive unit size of approximately 100 – 800 nm in diameter. Mycoplasma cells replicate by binary division. On the basis of phylogenetic studies, mycoplasmas belong to the clostridia [7,8].

They form a unique group of bacteria, characterized by lack of a rigid cell wall. On their surface there is a triple-layered membrane containing proteins and lipids. The majority of the membrane is made of cholesterol, which is responsible for the osmotic fragility of bacterial cells. Because of the plasticity of the membrane, mycoplasmas could exhibit a wide variety of morphologies including pear and flask shapes (Fig.1) [7,9]. Mycoplasma cells contain only minimum other organelles for the growth [8].

Mycoplasmas have the smallest genome among prokaryotes with low guanine and cytosine contents (24-40%). The complete genome sequences of *M. pneumoniae, M. genitalium, M. penetrans* and *M. pulmonis* have been reported previously and their sizes range from 0.57 to 2.2 Megabases (Mb), which is fairly small, compared, for example, to the 4.64 Mb of *Escherichia coli.* This reduced genetic information
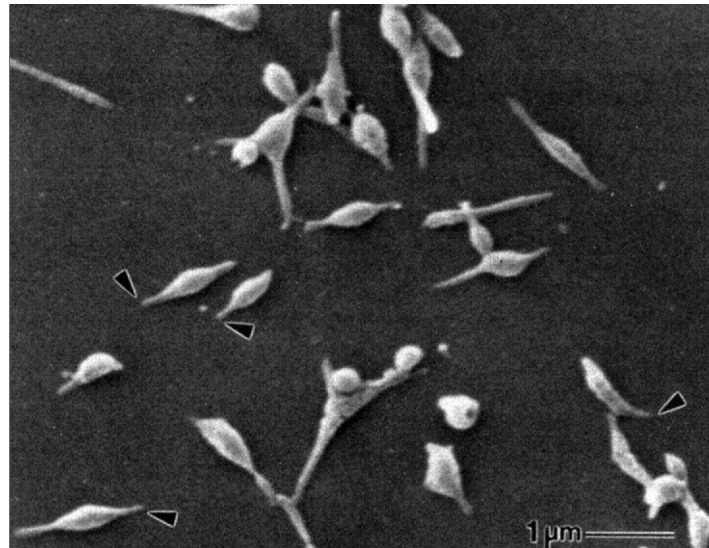

Figure 1. Scanning electron micrograph of *M. pneumoniae* cell (reprinted from reference 9)

codes only for a limited number of metabolic and biosynthetic pathways and is responsible for many characteristics of mycoplasmas, such as parasitic life or fastidious growth. Mycoplasmas are also characterized by a high genetic heterogeneity, which is caused predominantly by mutations leading to a wide spectrum of variations in genome size within the same species [8,10,11].

Pathogenetic mechanisms of mycoplasmas are currently intensively studied. It was reported that the major virulence factor is considered to be an adherence and close contact with the host cell.

Mycoplasmas are not found freely living because they depend on a host cell to supply the necessary nutrients. Several reports have also documented cytotoxic effect on the host cell by peroxides and other products of mycoplasma metabolism, causing oxidative damage to the host cell membrane [8,11,12]. The other possibility is the interaction with host immune cells and induction of an autoimmune reaction. Mycoplasmas may directly activate cytokine production from peripheral blood leukocytes, epithelial cells or macrophages and induce inflammatory response. Several mycoplasma species, such as *M. penetrans*, have also an ability

to actively penetrate into a variety of different types of mammalian cells, many with minimal phagocytic ability [11].

The laboratory diagnosis of mycoplasmas from clinical samples is based on direct methods. The "gold" standard of detection for mycoplasma cells is the cultivation technique on a selective-diagnostic medium enriched with horse serum and yeast extract (Fig.2). The culture methods are sensitive but time-consuming. The incubation times needed for such diagnosis of mycoplasmas range from 2 to 8 days. Other diagnostic procedures include molecular biology methods, such as polymerase chain reaction and its modifications, or DNA-hybridization. Serology has been the most common laboratory option for the detection of acute *M. pneumoniae* infections [13,14].

Figure 2. Colony of *M. hominis* on the PPLO agar (magnification 125x)

Mycoplasmas are naturally resistant to those antibiotic compounds, which are directed to the inhibition of cell wall synthesis, such as penicillins or cephalosporins. The drugs of choice for the treatment of mycoplasma infections are tetracyclines, which inhibit proteosynthesis. Another therapeutic approach is to use either new generation macrolides, such as azithromycin and clarithromycin, or fluoroquinolones. Recently, a lower sensitivity of isolated strains against antibiotics has been reported. Higher resistance of mycoplasma to antimicrobial agents is due to mutations in antibiotic targets [15,16]. The other possibilities of the antimycoplasmal treatment could be natural substances, as were reported previously [17].

Mycoplasma pneumoniae

M. pneumoniae is an obligatory human pathogen, responsible for acute infections of the upper and lower respiratory tracts. It is one of the most common etiological agents of community-acquired pneumonia (CAP) in children and young adults, but disease may occur in any age group. *M. pneumoniae* is transmitted by aerosol from person to person or by close contact (e.g. schools, hospitals, military barracks) [18,19]. The disease transmission punctuated worldwide with cyclic epidemics every 3 to 5 years. Although the incidence of disease does not vary significantly in season, the greatest proportion of patients with pneumonia due to *M. pneumoniae* infection is during summer in temperate climates [9]. The incidence of CAP caused by *M. pneumoniae* is up to 20% of all cases and is responsible for approximately 3-18% of cases in patients who require hospitalization [20].

The incubation period of the CAP is 2 to 3 weeks. Up to 20% of the respiratory infections caused by *M. pneumoniae* may be asymptomatic. The signs of symptomatic *M. pneumoniae* infections are often minimal. Low physical sings in comparison with significant roentgen findings are typical. Clinical

manifestations include dry cough, high fever and flu-like symptoms. Separate studies indicate that *M. pneumoniae* can precipitate asthma symptoms, but the exact role in this pathogenesis remains unclear [21,22].

Infections caused by *M. pneumoniae* are commonly associated with extra-pulmonary manifestations. In 25% of *M. pneumoniae* infections, gastrointestinal symptoms (nausea, diarrhea, vomiting) have been described. Other clinical extra-pulmonary symptomatology involving central nervous system, such as encephalitis and meningoencephalitis have been reported as well [23]. Complications affecting cardiac, hepatic, renal, skin and muscular systems (erythema multiforme) were reported less frequently [9].

Several diagnostic methods are used to detection of *Mycoplasma pneumoniae* infection. The traditional groups of them are serologic techniques, especially complement fixation test, detection of cold agglutinins or enzyme-linked immunoassays. Commercially available serologic tests detect a rise of IgG titre in paired sera or specific IgA and IgM in acute phase serum. A fourfold or greater rise in antibody titer indicates a current or recent infection. The molecular biology methods such as PCR are the other possibility of laboratory detection of *M. pneumoniae* in the respiratory secretions. Isolation of the *M. pneumoniae* by culture methods is not routinely performed, because of low sensitivity and time-consumption [9,13].

Mycoplasma hominis

This *Mycoplasma* species frequently colonizes the urogenital tract and is associated with various infections in genitourinary system in men and women. The prevalence of *M. hominis* is between 10-20% for men and 20–40% for women. An increased occurrence of this pathogen is significantly associated with both socioeconomic conditions and sexual activity [15,24].

M. hominis is generally genitourinary pathogen linked with inflammation of the mucosal epithelium in the genital system. *M. hominis* is frequently isolated from samples in cases of nongonococcal urethritis, cervicitis, cystitis, salpingitis, chorioamnionitis or bacterial vaginosis. Inflammatory processes in pregnant women represent common pathways that could lead to complicated pregnancy and initiate a premature

spontaneous delivery. Colonization of the genital system by *M. hominis* may lead to complications such as stillbirth, low birth weight or perinatal mortality [24].

These mycoplasmas have also been implicated in several cases of unexplained infertility. Many studies have described an association between the isolation of *M. hominis* from sperm and low sperm quality in men. Several studies have reported a negative effect of *M. hominis* mainly on semen concentration and abnormal sperm morphology. The impact on semen parameters and male infertility remains unclear [25].

M. hominis is reported to rarely induce extra-genitourinary complications particularly in the neonates, immunosuppressed or predisposed subjects. It has been described as the causative agent of diseases in the central nervous system (brain abscesses, meningitis) or in the respiratory tract (pneumonia) [26,27,28].

Laboratory diagnosis of *M. hominis* infections has been traditionally accomplished by culturing the pathogen on the various specialized media and identification of characteristic morphology of colonies or on the basis of biochemical properties. Molecular assays proved to be rapid, sensitive and more specific than culture diagnostic purposes. Despite these advantages, culture remains the most economical and practical means for detection of *M. hominis*. PCR can be performed in different urogenital samples, amniotic fluids and respiratory tract specimens from newborns [27]. Serological test methods for the detection of *M. hominis* include ELISA and metabolism inhibition, but the high incidence of this pathogen in healthy people makes interpretation of antibody titers against *M. hominis* difficult [29].

Mycoplasma genitalium

M. genitalium is another sexually transmitted pathogen from the genus *Mycoplasma*. It is commonly associated with urogenital infections. However, this species has been detected also in respiratory or rectal specimens [30,31,32].

Clinical manifestations of *M. genitalium* infections in women are urethritis or salpingitis. *M. genitalium* is often cited as a possible etiological agent of pelvic inflammatory disease (PID). Several studies have linked this species to acute endometritis and mucopurulent cervicitis [31].

In men, *M. genitalium* has been reported as the causative agent of non-gonococcal urethritis (NGU). It is detected in about 10-15 % of cases of NGU and has been also linked to balanoposthitis (inflammation of glans penis and prepucium). Several studies have indicated a role of *M. genitalium* in chronic persistent prostatitis and also in a malignant transformation of benign human epithelial cells, especially during chronic infections [33,34].

Other pathogenic mycoplasma species

Some mycoplasma species are frequently isolated from immunosuppressed patients or patients with human-immunodeficiency-virus (HIV) infection. Many studies reported *M. penetrans* and *M. fermentans* as additional mycoplasma pathogenic species in humans, causing infections of the urogenital or respiratory tracts. Ability of this microorganism to penetrate into the host cells is well known [11,35].

Epidemiological data have shown a high frequency of both species colonization in HIV-infected patients. The potent stimulating activity of *M. penetrans* on T lymphocytes from HIV-infected individuals is of a particular interest in the view of supposed contribution of the immune activation to HIV replication and disease progression. However, *M. penetrans* was also isolated from the blood and throat of a non-HIV-infected patient with primary antiphospholipid syndrome [36,37]. *M. fermentans* was isolated from the synovial fluid in arthritis patients and may well prove to be important in the etiology of such diseases [38]. Moreover, chronic infections caused by *M. fermentans* and *M. penetrans*, might apparently induce chromosomal instability and malignant transformation of mammalian cells [39].

CONCLUSION

Mycoplasmas represent a significant group of opportunistic pathogenic microorganisms, which are involved in infections of epithelial cells in humans and animals.

Mycoplasma infections in humans are associated with inflammatory processes involving various systems, mainly in genitourinary and respiratory tracts. Particularly immunosuppressed patients and newborns are susceptible to such infections but diseases caused by mycoplasmas can occur at any age.

It has also been reported that chronic nature of mycoplasma infections could generate chronic inflammation with a cancer-inducing, immuno-suppressive effect and can induce autoimmune diseases. Recently, mycoplasma infections of the urogenital system have been intensively studied because of their potential role in human infertility.

ACKNOWLEDGEMENTS

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