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BRIEF REPORT

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Isolation of *Mycoplasma hominis* in critically ill patients with pulmonary infections: clinical and microbiological analysis in an intensive care unit

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Abstract *Objective: Mycoplasma hominis* is a well recognized extragenital pathogen. However, it is an uncommon cause of respiratory infections in critically ill patients admitted to the intensive care unit (ICU). *Design and setting:* Prospective clinical investigation in a 21-bed ICU in a university hospital. *Patients:* Seven patients requiring intensive care who developed a ICU-acquired pneumonia in which *M. hominis* was recovered from bronchoalveolar lavage and pleural fluid cultures. *Interventions: M. hominis* was isolated in all patients by use of conventional bacteriological cultures. All strains were identified by 16S rRNA gene sequencing analysis. Patients' charts were reviewed for each case of infection. *Results:* Seven strains of *M. hominis* were isolated during a 4-year period. All of these isolates were recovered from adult men admitted to the ICU and all had clinical signs of pneumonia. In three patients treatment for *M. hominis* with quinolones was associated with a good clinical response. *Conclusion:* Suspicion of *M. hominis pneumonia* must be heightened particularly in critically ill patients. Therefore an understanding of the microbiology of this organism is essential to successfully treat patients with these infections that are not ordinarily covered with standard antibiotic therapy.

Keywords *Mycoplasma hominis* · Pneumonia · Intensive care unit

Introduction

Patients admitted into intensive care units (ICUs) are at a great risk for acquiring nosocomial infections due to their critical conditions and weakened immune system [1]. Ventilator-associated pneumonia (VAP) is the most frequent nosocomial infection in the ICU and occurs in roughly 25% of patients requiring mechanical ventilation (MV) for more than 48 h [2, 3]. *Mycoplasma hominis* is a commensal inhabitant of the lower urogenital tract in many sexually active adult men and women [4]. However, it may also cause localized extragenital disease. Host predisposing factors such as immunosuppression, malignancy, trauma, and complications related to urogenital manipulations or surgery are considered to be associated with extragenital mycoplasma infections [5]. The recognition of infections by *Mycoplasma* species in critically ill patients is important because β-lactam and aminoglycoside antibiotics, which are usually used in empirical antibiotic therapy, are not effective against these organisms. Pneumonia caused by *M. hominis* is very rare, but since the true incidence of infections caused by this pathogen is unknown, its real importance may be underestimated. Recognition of the morphological characteristics of mycoplasmas on bacteriological culture media may increase the recovery of these organisms in atypical clinical settings [6]. Here we describe the clinical and microbiological features of seven isolates of *M. hominis* in critically ill patients who acquired pneumonia during their hospitalization to the ICU. The case of one of these patients has been previously reported [7].

Patients and methods

Patients

Between April 2000 and December 2004 seven patients were found to have respiratory infections by *M. hominis* in three ICUs at the University Hospital Marqués de Valdecilla. All of these isolates were recovered from adult men who presented clinical signs of pneumonia as well as images of pulmonary infiltrates on chest radiography, temperature of 38 °C higher or of 36.5 °C or lower, peripheral leukocyte count greater than 11,000 or less than 5,000 cells/μl, and the presence of purulent secretions.

Specimen processing and isolates

Pleural fluid and bronchoalveolar lavage (BAL) specimens were processed by standardized methods [8] and were tested for Gram-stain and aerobic-anaerobic culture. The incubation time extended for up to 72 h. Owing to the morphology and size of the colonies and the fact that Gram-stained smears showed no micro-organisms, the presence of *Mycoplasma spp.* was suspected, and colonies were therefore subcultured into UMM lyo broth with Mh supplement (Mycofast Evolution 2 International Microbio Signes, France). Definitive identification was determined by automated DNA sequencing of 16S rRNA gene and sequence comparison from sequences available from the GenBank Nucleotide Sequence Database [9]. In addition, all samples were tested for the presence of other respiratory pathogens, such as *Legionella*, fungi, mycobacteria, and viruses.

Antibiotic susceptibility testing

A broth microdilution method for determination of the minimal inhibitory concentration was performed using Sensititre panels (TREK Diagnostic Systems. Cleveland, Ohio, USA) [10]. Erythromycin resistance was confirmed by the Etest method (Biodisk, Solna, Sweden) [11].

Results

Demographic information, clinical and microbiological findings, and outcomes of the seven cases are summarized in Table 1. The patients' median age was 46 years (range 25–65). No patient had a respiratory tract infection when admitted to the ICU and all had been treated with empirical antibiotic therapy prior to diagnosis of pneumonia due to prophylaxis after lung transplant, multiple trauma or sepsis. Four patients required MV for postoperatory situation, polytraumatism, sepsis, and coma, and three patients were weaned off MV prior to pneumonia. Symptoms of pneumonia started 96 h or later after hospitalization in the ICU. In all patients BAL were obtained when the start of pneumonia symptoms was observed, after which empirical antibiotic therapy was administered. In addition, pleural fluids were obtained on patient numbers 5 and 6 when empirical antibiotic therapy had been started. *M. hominis* was the only pathogen isolated from the site of infections in four cases and was associated with a copathogen in the remaining three (Table 1). *M. hominis* diagnosis took an average of 8.4 days (range 6–17 days) after the collection of respiratory samples. *M. hominis* was not recovered in blood cultures performed at the beginning of pneumonia symptoms. Results for *Legionella*, fungi, mycobacteria, and virus cultures all were negative. Urines were cultured specifically only for urogenital mycoplamas in three patients and *M. hominis* along with *Ureaplasma urealyticum* was isolated from two of them. The sensitivity of *M. hominis* isolates to the different antibiotics tested is given in Table 2. Once *M. hominis* was diagnosed, empirical treatment was changed to an effective antibiotic, except in patient numbers 4 and 7, in whom *M. hominis pneumonia* was diagnosed postmortem. The clinical course was torpid in all of them, although in patient numbers 2, 3, and 5 the specific treatment for *M. hominis* with quinolones for 2 weeks was associated with a good clinical response. In patient number 1, *M. hominis* diagnosis and treatment change to quinolone was made 2 days before its death. Autopsies confirmed the causes of death (Table 1).

Discussion

M. hominis is generally considered an opportunistic agent that causes invasive infections in susceptible populations [12, 13]. Accordingly, critically ill patients in ICUs could be more receptive to be infected because of their decreased immunity and frequent use of invasive procedures. VAP, the predominant infection in ICUs, is most commonly due to potentially multiresistant bacteria [14], and consequently prevention and control strategies have focused on methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, *Pseudomona aeruginosa*, *Acinetobacter* spp., and extended-spectrum β-lactamase-producing Gram-negative bacilli, among others. Outcome of patients with ICU-acquired pneumonia depends on the adequacy of early empirical antibiotic therapy [3, 15] which is often based on timing of its occurrence in relation to the onset of MV. *M. hominis* is intrinsically resistant to β-lactams, macrolides, aminoglycosides, and glycopeptides which are commonly used as empirical therapy in ICU infections. The real incidence of pneumonia caused by *M. hominis* in ICU is unknown and seems to be underestimated. In our center 512 samples of BAL or pleural fluid were tested by conventional bacteriological culture between 2000 and 2004. The incidence of

Table 1 Selected demographic data, clinical and microbiological findings, and outcome in seven male patients with *Mycoplasma hominis* infections during ICU hospitalization. (*ICU* intensive care unit, *BAL* bronchoalveolar lavage, *PDA* parenteral drug addict, *COPD* chronic obstructive pulmonary disease, *piper/tazob* piperaciline-tazobactam, *MOF* multiple organ failure)

Patient no.	Age (years)	Prior illness, risk factors	Date and reason for admission to ICU	Initial therapy on admission	Delay between ICU admission and nosocomial pneumonia (days)	Initial empirical treatment	Site of *M. hominis* isolation and copathogens	Delay between respiratory samples and microbiological diagnosis of *M. hominis* (days)	Modified therapy	Outcome
1	65	Pulmonary fibrosis	May 2000; postoperatory left lung transplantation	Piper/tazob, clindamycin, gentamycin	6	Piper/tazob, gentamycin, Gancyclovir	*M. hominis* (BAL)	17	Ciprofloxacin	Died the 25th day after transplantation for diffuse pulmonary hemorrhage
2	25	No risk factors known	October 2001; polytraumatism	Piper/tazob	6	Piper/tazob, ciprofloxacin	*M. hominis* (BAL)	6	Ciprofloxacin	Resolved the 21th day after admission
3	46	Hypertension, alcoholism	March 2002; subarachnoid hemorrhage	Piper/tazob	6	Piper/tazob	*M. hominis* (BAL)	6	Levofloxacin	Resolved the 23th day after admission
4	42	Esophageal carcinoma, tracheoeso-phageal fistula	April 2003; septic shock	Imipenem	4	Imipenem	*M. hominis*, *P. aeruginosa* (BAL)	8	No	Died the 9th day after admission for septic shock with MOF
5	36	PDA hepatitis C	August 2003; polytraumatism	Cefepime, teicoplanin	9	Cefepime, levofloxacin	*M. hominis* (BAL)	7	Levofloxacin	Resolved the 25th day after admission
6	54	Bipulmonar transplant	July 2004; postoperatory bronchial dehiscence reintervention	Vancomycin, amikacin	13	Linezolid, tobramicin	*M. hominis*, *P. aeruginosa* (pleural effusion)	8	No	Died the 49th day after admission for primary graft failure
7	61	Severe COPD and emphysema	December 2004; postoperatory Bilateral lung transplantation	Piper/tazob	12	Imipenen, amikacin, voriconazole	*M. hominis* (left pleural effusion), *M. hominis* /*A. baumannii* (right pleural effusion)	7	No	Died 24 days after transplant-ation for diffuse pulmonary hemorrhage

Table 2 Antibiotics tested for *Mycoplasma hominis* isolates. The Clinical Laboratory Standard Institute has not yet published official breakpoints for *Mycoplasma*; for this reason resistance and susceptibility were defined according to those established for fastidious organisms (*MIC* minimal inhibitory concentration, *R* resistance, *S* susceptible)

Antibiotics tested for the *Mycoplasma hominis* isolates	MIC (μg/ml)
Doxycycline	< 4 (S)
Tetracycline	< 2 (S)
Minocycline	< 4 (S)
Clindamycin	< 2 (S)
Erythromycin	> 32 (R)
Azithromycin	> 4 (R)
Levofloxacin	< 0.5 (S)
Ofloxacin	< 1 (S)
Ciprofloxacin	1 (S)
Moxifloxacin	0.25 (S)
Gentamycin	> 4 (R)
Quinupristin-dalfopristin	2 (S)
Chloramphenicol	8 (S)
Rifampicin	> 2 (R)

M. hominis pneumonia was estimated to be 1.3% among samples tested.

In patients admitted to the ICU the presence of an invasive device as orotracheal tube or urethral catheters increases the risk of infection by favoring the access of micro-organisms into a normally sterile space. The origin of the *M. hominis* infection in these patients is unknown. A possible explanation is microaspiration of oropharyngeal contents, but we consider that our isolates of *M. hominis* did not represent oropharyngeal contamination because the proportion of squamous epithelial cells, as indicator of oropharyngeal contamination, was less than 1% in all episodes. Morever, all specimens showed heavy growth of *M. hominis* in cultures. We also excluded other causes to explain clinical signs of pneumonia, such as a lesional edema complicating a thoracic trauma, a reperfusion injury after lung transplantation, and a lung transplant rejection.

A possible alternative source of infection is mycoplasmaremia from the colonized urogenital tract and secondary to urethral catheterization. Unfortunately, we did not obtain urine or urethral discharge samples from all of our patients in order to investigate the presence of urogenital mycoplasmas. *M. hominis* was not recovered in blood cultures since mycoplasmas cannot be detected by routine blood culture systems, probably due to the mycoplasmastatic effects of the sodium polyanethol sulfonate, the anticoagulant widely used in liquid blood culture media [16, 17]. Suspicion of *Mycoplasma* infection must be heightened particularly in critically ill patients for whom there are findings of purulence in the face of negative results from cultures and smears. Nevertheless, VAP is polymicrobial in nearly 40% of critically patients [18]. In our series the concomitant *P. aeruginosa* and/or *A. baummanii* isolation diminished the importance of the pathogenic role of *M. hominis*.

One factor that is potentially associated with a more severe outcome for patients with polymicrobial infections would be the inappropriateness of initial antibiotic therapy, with some bacterial species escaping the spectrum of initial empirical therapy. Antimicrobials agents that interfere with protein synthesis, such as tetracyclin and clindamycin, and those that inhibit DNA replication, such as quinolones, are considered effective against *M. hominis*. In three patients the specific treatment for pneumonia with quinolones was associated with a good clinical response. Linezolid has also proved to have some activity [19], but it was not assayed in this work. There is evidence suggesting that excessive mortality due to the administration of inappropriate antibiotics is not reduced by correction of regimens when culture results are available later [9, 20]. Although it is difficult to believe that *M. hominis pneumonia* was the cause of death in the four patients, these infections may have contributed to increased suffering and costs for patients in the form of prolonged stays.

Although *M. hominis* can grow on conventional microbiological media, more specific laboratory methods and a prolonged period of incubation should be used in case this organism is suspected. Although methods are available for molecular detection of specific agents involved in determined respiratory infections (e. g., multiplex polymerase chain reaction for detection of atypical pneumonia agents), similar assays for the empirical detection of unexpected pathogens responsible for cases of undetermined pneumonia are currently unavailable. Recognition of the potential for *M. hominis* to cause pneumonia should prompt request for special microbiological studies, especially in critically ill patients who present with pulmonary infiltrates and negative cultures for respiratory pathogens, despite the presence of neutrophils on Gram's stains of respiratory tissue or fluid specimens. In summary, it is prudent to consider *M. hominis* as a potential opportunistic pathogen in acquired pneumonias in ICUs, while further research is needed to increase our understanding in the epidemiology and the outcome of this unusual infection.

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