Clinical and microbiological characteristics of pleuro-pulmonary infection due to *Streptococcus intermedius*

**ABSTRACT**

The clinical and microbiological characteristics of pleuro-pulmonary infection (PPI) caused by *Streptococcus intermedius* is described, including 6 cases in the literature and 9 cases handled at the present centre. Out of the 15 patients, 12 were male; mean age at diagnosis was 62.06 ± 15 years. Twelve had risk factors for *S. intermedius* infection such as alcoholism in 5 (35.7%) patients, periodontal disease in 3 (24.6%) cases, chronic obstructive pulmonary disease in 3 (24.6%), and diabetes mellitus in 2 (14.2%). Cough was present in 12 (80%) patients and chest pain and dyspnea in 9 (60%). The mean diagnosis interval was 34 days. The diagnosis was obtained from pleural fluid aspirate in 13 (86.6%) cases and from biopsy/tissue samples in 2. The most frequently antimicrobials used for treatment were ceftriaxone + levofloxacin. Ten patients cured with a combination of medical and surgical treatment and 2 patients died as a consequence of infection. The incidence of PPI caused by *S. intermedius* is increasing in our health area; drainage along with antibiotic therapy is recommended for treatment.

Key Words: Pleuro-pulmonary infection, *Streptococcus intermedius*, pleural effusion, antimicrobials, drainage.

**INTRODUCTION**

Pleuro-pulmonary infection (PPI) is a common entity which are mainly caused by bacteria. A wide range of microorganisms can cause PPI, although the most common bacteria that are involved in immunocompetent adults in the community acquired setting include *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, viruses and...
Chlamydia pneumoniae [1]. In elderly patients and in those with other underlying diseases Haemophilus influenzae, Legionella pneumophila and Moraxella catarrhalis may be also causes of PPIs [1]. Streptococcus milleri group is mainly associated with abscesses and supurated infections and is an uncommon cause of PPI. This group is currently known as Streptococcus anginosus group (SAG), term suggested by Kawamura et al. [2], and includes S. anginosus, S. constellatus, and S. intermedius. Of them, S. constellatus is generally isolated from samples of respiratory tract. However, S. intermedius is mainly involved with both liver and cerebral abscesses [3,4]. Until now, only few cases of PPI due to S. intermedius have been reported in the medical literature [5-10]. Another study shows 14 patients with PI due to S. intermedius in a period of 10 years [11].

In the last 3 years, we have diagnosed in our laboratory 9 cases of PPI caused by S. intermedius. Due to its rarity, the literature has provided only limited guidance on the characteristics of patients with this condition, so a review was performed on diagnostic and therapeutic approaches to this entity.

METHODS

We describe 15 patients with PPI due to S. intermedius. Using the key words “Streptococcus intermedius pleural infection” and “Streptococcus intermedius pulmonary infection” we searched MEDLINE (National Library of Medicine, Bethesda, MD), Web of Science, CINAHL, and Cochrane systematic review databases for case reports of this condition. We also checked the references cited in the papers for additional case reports published before 1966.

We traced 6 cases caused by S. intermedius and described in sufficient detail. These cases, along with our 9 patients, are the basis of the present report. Data on age and sex, risk factors or underlying diseases, time until diagnosis, clinical manifestations, radiological and laboratory findings, microbiologic diagnosis, treatment, outcome and follow-up were recorded over a period of two years (June 2015–June 2017).

In the microbiology laboratory the pleural fluid was processed as follows: after centrifugation, the sample was inoculated in blood agar (either aerobic or anaerobic) (BD Columbia Agar 5% Sheepblood®, Becton Dickinson), chocolate agar (BD Choco Agar, Becton Dickinson) and thioglycolate broth (BDTM Fluid Thiglycollate Medium, Becton Dickinson). All media were incubated at 37º C. A mass spectrometry method (Bruker Biotyper, Billerica, MA) was employed to identify the strain. All cases of S. intermedius infection in our laboratory were obtained in pure culture.

RESULTS

The first case of PPI due to S. intermedius here reviewed was published by Roy et al. in 1991 [5]. A review of the medical literature identified 29 cases of PPI caused by this pathogen. Fourteen cases were excluded because no individualized data were available [11]. This review therefore comprised 15 patients, including our cases.

General characteristics. Table 1 summarizes the clinical and microbiologic findings for the 15 patients, and table 2 compiles the features of pleural effusion. There were 12 (80%) men and the mean age of patients was 62.06 ± 15 years (range: 38-89 years). The mean interval from clinical onset to infection diagnosis was 34 days (range: 3 to 150 days). This interval was not reported for one patient [9].

No risk factors for Streptococcal infection were found in one patient (6.6%). Major risk factors for Streptococcal infection were alcoholism in 5 (33.3%) patients, chronic obstructive pulmonary disease and periodontal disease in 3 (20%) cases each one, and diabetes mellitus in 2 (13.3%). Thirteen (86.6%) patients were smokers and 3 (20%) patients had more than one risk factor for this infection.

Empyema was seen in 7 (46.6%) patients, and both pneumonia and pleural effusion in 2 patients each one (13.3%).

Clinical manifestations. Cough was reported by 12 (80%) patients, and chest pain and dyspnea by 9 (60%) patients each one. Finally, fever was recorded in 8 (53.3%) patients. Five patients (33.3%) had two symptoms, while 10 (66.6%) had three or more symptoms.

Microbiology and laboratory findings. At the diagnosis of PPI, data on C-reactive protein (CRP) level were not reported in 6 (40%) patients and data on white blood cell (WBC) were not reported in only 2 (13.3%). The mean CRP level was 208.6 mg/L (range: 33.6-480), and the mean WBC level was 21,418/mm³ (range: 3,130-40,000).

Regarding data on pleural fluid, protein level was elevated in all patients tested, except for one patient (case 10); the mean protein level was 4 g/dL (range: 1.7-5.2). LDH level was also elevated in all patients tested (n=11), being the mean LDH level 2777 g/dL (range 571-6280). Finally, the mean white cell count level was 89,484 mm³ (range 370-466,000).

S. intermedius was diagnosed by culture of pleural fluid (PF) aspirate in 13 (86.6%) cases, and culture of biopsy or tissue samples in 2 (13.3%).

Susceptibility tests for S. intermedius were reported in 12 (80%) isolates (table 3). Antimicrobial susceptibility was completely performed in cases 7 to 15. In these 9 cases, 100% of isolates were susceptible to cefotaxime, levofloxacin, linezolid, vancomycin and daptomycin, and 45.5% of isolates were resistant to both clindamycin and erythromycin. Only one strain of S. intermedius was intermediate to penicillin (case 7; MIC 1 mg/L). In case 4, susceptibility to levofloxacin was reported, and in cases 5 and 6 susceptibility to penicillin was also reported.

Antimicrobial and surgical treatment. Fourteen (93.3%) patients underwent antibiotic treatment, with a single drug in 2 cases (14.2%), with two drugs in 8 cases (57.1%) and
| Patient (year of publication) | Age (years)/sex | Clinical manifestations | Risk factors | Time until diagnosis (days) | Radiological findings | Laboratory findings | Microbiologic diagnostic | Antimicrobial treatment | Other treatments | Outcome/follow-up (months) |
|-------------------------------|-----------------|------------------------|--------------|-----------------------------|----------------------|--------------------|------------------------|-------------------------|------------------------|--------------------------|
| 1 (1991) Roy [5]              | 38/M            | Chest pain, cough, dyspnea, fever, lightheadedness | Smoker Caries | 7                           | Large left pleural density | WBC 12,600/mm³ | Pleural fluid culture | Cefotaxime Penicillin | Drainage Thoracotomy + decortication | Cure/3                  |
| 2 (2000) Khatib [6]           | 55/M            | Fever, cough, hemoptysis, headache | Alcohol cirrhosis | 10                          | Right upper-lobe consolidation | NR                | Lung biopsy culture | Ceftriaxone + ampicillin | NR                     | Died                     |
| 3 (2000) Mautner [7]          | 80/M            | Chest pain, cough, fever, shortness of breath | Smoker | 14                          | Left hemithorax opacification | WBC 22,000/mm³ | Pleural fluid culture | NR                      | Drainage Thoracotomy + decortication | NR                      |
| 4 (2006) Lokandar [8]         | 52/M            | Cough, shortness of breath, loss weight | Smoker Caries, gingivitis | 150                         | Localized pleural effusion | NR                | Pleural fluid culture | Levofloxacin + clindamycin | Drainage | Cure/5                  |
| 5 (2014) Noguchi [9]          | 79/M            | Fever, cough | Empyema 4 months ago Smoker Drinker Poor oral hygiene | NR | Left hemithorax opacification | WBC 39,600/mm³ | CRP 33.6 mg/dL | Pleural fluid culture | Meropenem | Drainage Pleurectomy | Improved/New NR |
| 6 (2016) Hannooni [11]        | 52/F            | Cough, shortness of breath, fever | Asthma Smoker | 42                          | Bilateral multifocal lung infiltrate Localized pleural effusion | WBC 29,200/mm³ | Tissue sample culture | Erythromycin Ciprofloxacin + vancomycin + azithromycin Ceftriaxone | Drainage Pleurectomy + decortication | Cure/3                  |
| 7 (PR) Cobo                   | 75/M            | Cough, dyspnea, chest pain, hemoptysis | Asthma COPD | 5                           | Right hemithorax opacification | WBC 24,000/mm³ | CRP 200 mg/dL | Ceftriaxone Levofloxacin | Drainage | Cure/3                  |
| 8 (PR) Cobo                   | 63/M            | Cough, chest pain | DM Smoker COPD | 7                           | Pulmonary abscess and empyema Right hemithorax opacification | WBC 20,600/mm³ | CRP 353.7 mg/dL | Ceftriaxone Levofloxacin | Drainage | Cure/3                  |
| 9 (PR) Cobo                   | 62/F            | Fever, dyspnea | Smoker COPD Thoracic trauma | 2                           | Right basal pulmonary opacification Pleural effusion | WBC 20,080/mm³ | Pleural fluid culture | Ceftriaxone Levofloxacin | Drainage + pleural debridement | Cure/5                  |
| 10 (PR) Cobo                  | 89/M            | Increase of dyspnea, cough | DM | 15                          | Pulmonary empyema | WBC 18,520/mm³ | CRP 156.5 mg/dL | Pleural fluid culture | Ceftriaxone | Drainage | Cure/3                  |
| 11 (PR) Cobo                  | 48/M            | Dyspnea, fever, chest pain, cough, chills | Smoker Amigdalitis and cervical abscess | 5                          | Pulmonary abscesses Bilateral pleural effusion | WBC 3,130/mm³ | CRP 480 mg/dL | Ceftriaxone Levofloxacin | Drainage | Died                    |
| 12 (PR) Cobo                  | 72/M            | Cough, dyspnea, chest pain | Smoker Drinker | 3                           | Right basal opacification Pleural effusion | WBC 21,210/mm³ | CRP 284 mg/dL | Ceftriaxone Levofloxacin | Drainage | Improved/new pleural effusion 1 month later Cure/2 |
| 13 (PR) Cobo                  | 49/M            | Chest pain, dyspnea, fever | Smoker Drinker | 7                           | Right pleural effusion | WBC 40,000/mm³ | CRP 33.7 mg/dL | Ceftriaxone Clarithromycin Cefditoren | Drainage | Improved/new pleural effusion 15 days later Cure/1 |
| 14 (PR) Cobo                  | 74/M            | Chest pain, dyspnea | Smoker Drinker Pulmonary epidermoid carcinoma | 6                           | Right pleural effusion Nodular lesions in the right lung | WBC 15,100/mm³ | CRP 80.2 mg/dL | Imipenem Ceftriaxone Clindamycin | Drainage | Cure/2                  |
| 15 (PR) Cobo                  | 43/F            | Chest pain, cough, dyspnea | Smoker | 4                           | Left pleural effusion | WBC 12,400/mm³ | CRP 256 mg/dL | Levofoxacin | Drainage | Cure/2                  |

M: male; F: female; NR: not reported; PR: present report; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood count; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus
DISCUSSION

SAG is part of the normal biota of the oropharyngeal, urogenital, and gastrointestinal tracts [12]. These microorganisms are strongly associated with abscess formation in the brain, peritoneal cavity, and oropharynx [13], although *S. intermedius* and *S. constellatus* are generally more frequently associated with abscess formation than *S. anginosus* [14]. Moreover, it is well known that *S. anginosus* is frequently found in specimens from the urogenital or gastrointestinal tracts and *S. constellatus* can be found in infections of the respiratory tract or blood, as well as *S. intermedius* is most often identified in abscesses of the brain or liver [15].

PPI caused by *S. intermedius* is an uncommon event. Only few case reports with this condition have been published until now [5-10], and other report found some cases of this infection in a period of 10 years [11]. However, in our hospital we were able to trace 9 cases of PPI caused by this microorganism in the last 3 years, showing an increase of incidence of this infection in our health area. The main cause of this increase is unknown, but the use of new diagnostic tools such as MALDI-TOF techniques may be related to a better identification.

Risk factors for *S. intermedius* infection, including periodontal disease, diabetes mellitus, alcoholism and COPD [16] were recorded in 14 patients and may play an important role in the development of these infections. Moreover, 13 patients were smokers and, although the smoker status is not strictly a risk factor for this infection, this condition may lead to produce COPD in the future and to contribute to the infection. Once *S. intermedius* have entered the body, their pathogenicity has been attributed to their trend to form abscesses and suppurated infections [13,15].

Several mechanisms for *S. intermedius* infections have been suggested; among others, aspiration of oral secretions is of particular importance especially in elderly patients.

Table 2

| Patient* (year of publication) | Author [reference] | pH | Glucose (mg/dl) | Proteins (g/dl) | LDH (IU/L) in blood | WCC (mm³) | % neutrophils |
|-------------------------------|-------------------|----|----------------|----------------|-------------------|------------|--------------|
| 1(1991) Roy [5]               |                   | 7.04 | NR             | NR             | NR                | 370/NR     |
| 3(2000) Mautner [7]           |                   | 6.89 | 5              | 4.7            | NR                | 2,900/96   |
| 4(2006) Iskandar [8]          |                   | NR  | 10             | NR             | 6280              | 466,000/90 |
| 5(2014) Noguchi [9]           |                   | NR  | 1              | 4.3            | 2873              | NR         |
| 6(2016) Hannoondi [11]        |                   | NR  | 93             | 4              | 1372              | NR         |
| 7(PR) Cobo                    |                   | NR  | 1              | 2.8            | 3540              | 5,727/96   |
| 8(PR) Cobo                    |                   | NR  | 32             | 3.5            | 4860              | 63,298/95  |
| 9(PR) Cobo                    |                   | NR  | 1              | 3.9            | 1790              | 44,924/92  |
| 10(PR) Cobo                   |                   | NR  | 1              | 1.7            | 687               | 295,000/54 |
| 12(PR) Cobo                   |                   | NR  | 10             | 4.2            | 1535              | 19,212/91  |
| 13(PR) Cobo                   |                   | 7.5  | 1              | 5.2            | 2278              | 45,800/85  |
| 14(PR) Cobo                   |                   | 7.07 | 26             | 4.8            | 4762              | 38,552/82  |
| 15(PR) Cobo                   |                   | 7.2  | 74             | 4.7            | 571               | 2,548/32   |

Table 2. Pleural effusion characteristics from 13 patients with *S. intermedius* infection.

| Patient* (year of publication) | Author [reference] | pH | Glucose (mg/dl) | Proteins (g/dl) | LDH (IU/L) in blood | WCC (mm³) | % neutrophils |
|-------------------------------|-------------------|----|----------------|----------------|-------------------|------------|--------------|
| 1(1991) Roy [5]               |                   | 7.04 | NR             | NR             | NR                | 370/NR     |
| 3(2000) Mautner [7]           |                   | 6.89 | 5              | 4.7            | NR                | 2,900/96   |
| 4(2006) Iskandar [8]          |                   | NR  | 10             | NR             | 6280              | 466,000/90 |
| 5(2014) Noguchi [9]           |                   | NR  | 1              | 4.3            | 2873              | NR         |
| 6(2016) Hannoondi [11]        |                   | NR  | 93             | 4              | 1372              | NR         |
| 7(PR) Cobo                    |                   | NR  | 1              | 2.8            | 3540              | 5,727/96   |
| 8(PR) Cobo                    |                   | NR  | 32             | 3.5            | 4860              | 63,298/95  |
| 9(PR) Cobo                    |                   | NR  | 1              | 3.9            | 1790              | 44,924/92  |
| 10(PR) Cobo                   |                   | NR  | 1              | 1.7            | 687               | 295,000/54 |
| 12(PR) Cobo                   |                   | NR  | 10             | 4.2            | 1535              | 19,212/91  |
| 13(PR) Cobo                   |                   | 7.5  | 1              | 5.2            | 2278              | 45,800/85  |
| 14(PR) Cobo                   |                   | 7.07 | 26             | 4.8            | 4762              | 38,552/82  |
| 15(PR) Cobo                   |                   | 7.2  | 74             | 4.7            | 571               | 2,548/32   |

NR: not reported; LDH: lactate dehydrogenase; ADA: adenosin-deaminase; WCC: white cells count
Normal values: pH: 7.37-7.45; Glucose: >60 mg/dL; Proteins: 1-2 gr/dL; LDH: <50% plasma value; WCC: 1000-5000/mm³.

Cases 2 and 11 did not reported any data about pleural effusion

more than two in 3 (21.4%). Ceftriaxone plus levofloxacin was the antimicrobial regimen most used (5/35.7%).

Drainage of PF was performed in all patients, 9 of whom (60%) underwent only this procedure. Thoracotomy plus decortication was undertaken in 2 (13.3%) patients and pleurectomy in another 2 cases. Debridement was undergone only in one (6.6%) patient.

Outcome. The final outcome was not reported in one patient, and a favourable outcome was recorded in 12 (80%) patients after antibiotic plus surgical treatment. Two patients (13.3%) died. The follow-up was reported in 6 (40%) patients, with a mean time of 2.6 months (range 1-5 months).
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β-lactam agents. The treatment of choice for these infections has not yet been established but ceftriaxone seems to be the preferred antimicrobial used due to both an excellent activity

and tissue penetration. Regarding penicillin susceptibility, some strains intermediate with this antibiotic have been reported, and there are rare strains with resistance to penicillin [17]. Penicillin–intermediate or -resistant strains are more likely to be *S. anginosus* or *S. intermedius* than *S. constellatus* [17]. If allergy or resistance to β-lactam agents may be demonstrated, vancomycin is an appropriate alternative to treatment. Overall, fluoroquinolones are susceptible to SAG although MICs are high, but these microorganisms tend to develop resistance quickly and seems to be not appropriate for empirical treatment [18]. Most strains of the SAG are resistant to aminoglycosides and macrolide resistance appears to be increasing [17,19]. In the present study, 100% of susceptibility was obtained for cefotaxime, levofloxacin, linezolid, vancomycin and daptomycin, whereas only 55% of susceptibility was found for erythromycin and clindamycin. Only one isolate was intermediate to penicillin. Overall, susceptibility to several antibiotics is shown and antibiotic resistance in *S. intermedius* may be initially not considered a problem, although monitoring through susceptibility testing is advisable.

In the majority of cases, the diagnosis was carried out by culture of PF. In fact, drainage of pleural effusion was performed in all patients; other surgical procedures were pleurectomy, thoracotomy, decortication, and debridement.

The outcome was generally favourable and cure was documented in 10 patients. Two patients improved of the disease and in two cases the treatment fails and finally died as a consequence of the infection.

PPIs caused by *S. intermedius* are uncommon infections with few cases published in the medical literature. These infections tend to occur in males, smokers and with different risk factors such as periodontal diseases, alcoholism and COPD. The diagnosis may be suspected by elevation of CRP and WBC and must be confirmed microbiologically, taking samples of pleural fluid and/or lung tissue. Antimicrobial susceptibility testing of *Streptococcus* strains is also highly recommended. The association of antimicrobial drugs with drainage of pleural effusion is recommended to eradicate the infection.

**CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest

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None to declare

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