Clinical Features of Acute Respiratory Infections Associated with the Streptococcus Milleri Group in the Elderly

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Summary: The Streptococcus milleri group are becoming increasingly recognized as important pulmonary pathogens which may lead to the development of empyema or lung abscesses. Although several small series have been reported, the clinical and laboratory features of Streptococcus milleri infection have yet to be fully characterized in the elderly. We retrospectively examined the clinical features of 19 patients with Streptococcus milleri pulmonary disease who were admitted to our hospital between 2000 and 2002, based on their clinical records and laboratory data. The microbiological diagnosis was based on the results of quantitative sputum culture and other invasive procedures, including transthoracic needle aspiration or bronchoscopic examinations. There were thirteen cases of pneumonia, two of contaminant pneumonia and pleuritis, one of bronchitis, two of pulmonary abscess, and one of empyema. The patients ranged in age from 65 to 91. The most common symptoms at presentation were shortness of breath, coughing, sputum, and weight loss. An underlying disease existed in 14 of the 19 cases. We conclude that the Streptococcus milleri group is a more important cause of pulmonary infections than has been previously recognized.

Key words streptococcus milleri group, acute respiratory infection

INTRODUCTION

The term "Streptococcus milleri group" refers to a heterogeneous group of streptococci which are becoming increasingly recognized as clinical important pathogens. Streptococci that colonize the mouth and upper respiratory tract are generally harmless commensals [1]. These organisms are capable of causing disease (e.g., endocarditis or dental caries) and even death, especially when they gain entrance to host sites that are usually sterile [2], but they are rarely the cause of community-acquired pulmonary infections. In general, these oral commensals are distinct from the obvious pathogen Streptococcus pneumoniae, which may be found in the mouth and

upper respiratory tract of healthy persons but which frequently causes acute pulmonary infections [3]. However, one group of commensal oral streptococci, the Streptococcus milleri group, has been identified as an important cause of pulmonary empyema and abscesses [4,5]. There are numerous reports documenting the importance of the Streptococcus milleri group in respiratory infections [6-8].

We report the characteristics of 19 patients of advanced age with Streptococcus milleri pulmonary infections. The purpose of this study was to contribute to a better understanding of the importance of members of the Streptococcus milleri group as respiratory pathogens, by examining the epidemiological and clinical features of thoracic infections

caused by these pathogens in the elderly, especially in those of very advanced age.

PATIENTS AND METHODS

We retrospectively studied the clinical records of 19 patients of advanced age (over 65 years) who were diagnosed with acute respiratory infections caused by the *Streptococcus milleri* group and who had been admitted to our hospital between January 2000 and December 2002.

We clinically classified these acute respiratory infections as pneumonia, lung abscess, empyema or acute bronchitis. Specimens from patients were directly examined using the Gram stain and then plated onto a range of non-selective and enriched media for aerobic and anaerobic incubation. The plates were incubated at 37°C for up to five days. Any colonies with the colonial appearance and typical caramel odour of *Streptococcus milleri* were sub-cultured in carbon dioxide to check for enhanced growth.

For the diagnosis of acute respiratory infections caused by *Streptococcus milleri*, we adopted the Japanese guideline for *Streptococcus milleri* infections [9,10]; that is, *Streptococcus milleri* should be detected at a rate of at least 10⁶ CFU/ml of purulent sputum, gram-positive cocci phagocyted by polymorphonuclear leukocytes are detected, no other gram-positive cocci are isolated, and the infection subsides after the administration of antibiotics to which these pathogens are sensitive. When *Streptococcus milleri* was detected directly in a pleural effusion or transbronchial aspiration biopsy specimen, we diagnosed the patient as having a *Streptococcus milleri* infection. Furthermore we evaluated the severity of infection based on clinical evaluation methods for new antimicrobial agents [11].

RESULTS

Table 1 shows the clinical features of acute respiratory infection caused by the *Streptococcus milleri* group. *Streptococcus milleri* pulmonary infection

TABLE 1.
Characteristics of patients with respiratory infections caused by Streptococcus milleri

Case	Age	Sex	Diagnosis	Associated organisms	Underlying disease	Severity of infection	Treatment	Evolution
1	77	M	pneumonia	p. aureginosa	lung cancer	severe	cefazopran	death
2	77	M	pneumonia, pleuritis	(-)	pulmonary emphysema, liver cirrhosis	severe	flomoxef	death
3	79	F	pneumonia	(-)	bronchiectasis	moderate	sulbactam/cefoperazon	cured
4	87	F	lung abscess	(-)	(-)	moderate	ceftazidime+clindamycin	cured
5	80	F	pneumonia	(-)	(-)	mild	cefotiam	cured
6	79	M	pneumonia	(-)	(-)	mild	piperacillin	cured
7	91	M	pneumonia	(-)	heart failure	mild	cefotiam	cured
8	79	M	pneumonia	(-)	bronchiectasis	moderate	ceftazidime	cured
9	75	M	pneumonia	p. aureginosa	pulmonary emphysema, post operation of colon ca	severe	imipenem+clindamycin	death
10	65	F	pneumonia	(-)	(-)	mild	cefotiam	cured
11	78	M	pneumonia, pleuritis	(-)	lung cancer	moderate	sulbactam/cefoperazon	cured
12	79	F	pneumonia	(-)	(-)	moderate	cefotiam	cured
13	79	M	empyema	prevotella intermedia	pulmonary emphysema	severe	meropenem+clindamycin	cured
14	77	M	pneumonia	(-)	pulmonary emphysema	mild	sulbactam/cefoperazon	cured
15	73	M	lung abscess	bacteroides fragilis	pulmonary emphysema	moderate	ceftazidime+clindamycin	cured
16	80	M	bronchitis	(-)	bronchiectasis, DM	mild	cefotiam	cured
17	70	M	pneumonia	(-)	chronic hepatitis type C, DM	moderate	sulbactam/cefoperazon	cured
18	74	F	pneumonia	(-)	old pulmonary tuberculosis	mild	piperacillin	cured
19	65	M	pneumonia	(-)	chronic hepatitis type C, DM	severe	panipenem	cured

was identified in 19 patients, 13 men and 6 women, whose ages ranged from 65 to 91 years old. Thirteen of these patients had pneumonia, two had contaminant pneumonia and pleuritis, one had bronchitis, two had a lung abscess, and one had empyema. Severe, moderate and mild infections were observed in 5, 7 and 7 patients, respectively. None of them had bacteremia. Underlying diseases are also described in Table 1. They included 11 cases of pulmonary pathologies (lung cancer in 2 cases, pulmonary emphysema in 5 cases, bronchiectasis in 3 cases and history of pulmonary tuberculosis in 1 case), three of diabetes mellitus, three of liver disease and one of heart disease. However, five patients had no underlying diseases and none of them was alcoholic.

Microbiological diagnosis was made by culture of pleural exudate in 3 cases (patients 2, 11 and 13) and of bronchial lavage in 3 cases (patients 1, 11 and 14) (Table 1). Other cases of pneumonia or bronchitis were diagnosed based on the results of aspirated sputum culture. In 4 of the 19 cases, the infection was polymicrobial in nature. In infections related to a thoracic procedure, other organisms were also isolated: *Pseudomonas aeruginosa* and anaerobic bacteria (patients 1, 9, 13 and 15).

Antibiotics such as penicillin, cefem, carbapenem and clindamycin were administered to all patients. All the *Streptococcus milleri* isolates were suscepti-

ble to these antibiotics. With regard to evolution, 16 patients were cured and three patients died.

Table 2 shows the laboratory data and body temperature of the 19 patients. Severe cases tended to have a high WBC count, a high CRP value and high fever.

DISCUSSION

The *Streptococcus milleri* group is part of the usual flora of the mouth, but its actual prevalence is unknown. It is also found in normal faecal flora in 16-67% of healthy adults and has been isolated from normal appendix and from vaginal secretions [12-14]. The most important clinical feature of these microorganisms is their tendency to cause various suppurative infections such as dental abscesses or deep visceral abscesses [3,15,16].

In this study, of the various types of thoracic infections caused by *Streptococcus milleri*, empyema and lung abscesses were found to be the most common. This result agrees with previous reports by other authors [15,17,18]. Predisposing factors which have been associated with *Streptococcus milleri*, empyema and lung abscesses include mucosal disturbance (sinusitis, periodontal disease, enteric disease such as esophageal perforation), thoracic surgery, malignancy, neurological disease, alcohol abuse, and

TABLE 2.
Laboratory findings in 19 patients with Streptococcus milleri infection

Case	WBC (/ μ l)	CRP (mg/dl)	Total protein (g/dl)	Albumin (g/dl)	Body temperature ($^{\circ}$ C)
1	17270	14.4	6.8	3.0	38.6
2	15540	22.8	4.8	2.8	38.8
3	10940	9.6	5.9	2.8	37.5
4	9090	13.0	6.3	3.0	37.6
5	10340	3.6	6.4	3.4	37.4
6	8600	3.5	6.7	4.2	37.4
7	6310	3.6	5.9	3.3	37.5
8	9090	21.6	5.9	3.2	38.0
9	15570	18.7	6.4	3.7	38.4
10	8600	8.5	6.2	4.2	37.2
11	11720	5.9	6.1	3.3	37.6
12	14650	12.2	5.6	4.4	37.8
13	19020	23.3	5.6	3.0	38.8
14	7780	3.8	7.1	4.2	37.4
15	14960	18.3	6.1	3.2	37.8
16	11690	3.2	6.4	3.3	38.4
17	13600	10.3	6.6	4.1	37.8
18	9050	5.4	6.8	4.2	37.4
19	18500	21.9	5.4	2.3	38.4

diabetes [4,6,7,19]. Further, the underlying diseases observed were periodontal disease, diabetes mellitus, neoplasm, alcoholism, HIV infection and chronic obstructive disease; these associations have been recognized previously [3,20,21]. Our present study included only two cases of lung abscesses and one of empyema; most of the patients suffered from pneumonia. It is noteworthy that some of these cases of pneumonia were found in elderly people with neither underlying disease nor any predisposing factor.

Shinzato et al. [7] reported a possible synergy between the *Streptococcus milleri* group and anaerobic bacteria. The former organisms are often involved in mixed infections and their particularly frequent isolation in combination with anaerobic bacteria suggests synergy. It was also suggested that anaerobic bacteria might stimulate the growth of the *Streptococcus milleri* group and suppress the bactericidal activity of host cells [7]. In our study, we found two cases of mixed infections caused by *Streptococcus milleri* and anaerobic bacteria (patients 13 and 15). One had empyema and the other a lung abscess. We considered that these mixed infections might be one of the risk factors contributing to the severity of the infection, as suggested previously [3,7,22]. Furthermore, we had two patients with severe mixed infections caused by *Streptococcus milleri* and *P.aeruginosa* (patients 1 and 9). Patients with mixed pulmonary infections caused by *Streptococcus milleri* and another bacterial strain must be observed carefully. Our experience indicates that such mixed infections might be life-threatening.

Several authors have reported the results of treatment with antibiotics for infections caused by the *Streptococcus milleri* group and the susceptibility of the bacteria to some antibiotics [4,18,20,21,23]. There have been cases of resistance to penicillin [8,24], however, fortunately none of the isolates in our study showed decreased susceptibility to antibiotics (penicillin, β -lactam and clindamycin). Nevertheless, it is important to be aware of a possible resistance to antibiotics, and this may well become a more serious problem in the future.

It was reported that *Streptococcus milleri* was causative pathogen in about 3-15% of the cases of community-acquired pneumonia [25,26]. We had 15 cases of pneumonia associated with *Streptococcus milleri* in the elderly. We adopted the Japanese guidelines for the diagnosis of acute pneumonia and bronchitis caused by *Streptococcus milleri* in our study. However, it might be difficult to diagnose

Streptococcus milleri infections simply by examining sputum specimens. A further investigation will be needed to clarify diagnostic methods.

In this study, we reviewed 19 cases of acute respiratory infections caused by *Streptococcus milleri*. Although thoracic infections associated with *Streptococcus milleri* such as empyema and lung abscess are common, there were 15 cases of pneumonia among the 19 patients evaluated in this study. It has been shown that most such patients have underlying diseases or are alcoholics. However, we had 5 patients with no underlying disease and none of these five was alcoholic. *Streptococcus milleri* might become an important cause of acute pneumonia in patients of advanced age. The key principles of management of *Streptococcus milleri* infection are early diagnosis and control of the infection with appropriate antibiotics. It is important to select suitable antibiotics for these infections and prevent the progression to empyema or lung abscess, particularly in the case of mixed infections. We should be extremely careful in our management of mixed infections because of their severity.

We conclude that *Streptococcus milleri* must be recognized as a very important pathogen causative of acute respiratory infections, especially in elderly patients. Further prospective investigations are needed to provide additional details on the role of the *Streptococcus milleri* group in pneumonia and other lower respiratory tract infections.

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