Jpn. J. Infect. Dis., 61, 484-486, 2008

Short Communication

Clinical Analysis of Cases of Empyema Due to *Streptococcus milleri* Group

Yoshihiro Kobashi*, Keiji Mouri, Shinichi Yagi, Yasushi Obase and Mikio Oka

Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Kurashiki 701-0192, Japan

(Received February 25, 2008. Accepted September 8, 2008)

SUMMARY: In this study we analyzed 15 cases of empyema due to *Streptococcus milleri* group treated between January 2000 and December 2007. The majority (87%) were men, and the mean patient age was 62 years (range 36 to 83). An underlying disease was present in 14 of 15 cases. Six cases were complicated by pneumonia. Polymicrobial infection with *S. milleri* group was recognized in four patients. Most patients underwent chest tube drainage (87%), and all received antibiotic treatment (100%). The average duration of chest tube drainage was 8.4 days and that of antibiotic treatment was 14.0 days. Six cases (40%) underwent video-assisted thoracoscopic surgery for decortication. The duration of hospitalization was 19.6 days. The clinical effect of treatment was comparatively good (93%), and the prognosis was also good (mortality rate 7%).

Streptococcus milleri, a group that consists of the species *S. intermedius*, *S. constellatus*, and *S. anginosus*, is part of the normal flora of the mouth, gastrointestinal tract, and genitourinary system (1). There are some reports documenting the importance of the *S. milleri* group in the development of empyema and lung abscess. However, several series have recently described the clinical features of empyema development in these cases (2-4). In this study, we report the clinical characteristics of 15 cases of *S. milleri* infection (12%) among 126 cases of empyema encountered at Kawasaki Medical School Hospital (1,072 beds, Kurashiki, Japan) between January 2000 and December 2007.

Our respiratory specialists collected clinical data, including sociodemographics, clinical features, laboratory parameters, microbiology results, official radiographic reports, and outcomes such as length of hospitalization and mortality. All relevant diagnostic imaging of patients with confirmed empyema was reviewed independently.

Specimens of pleural fluid and sputum were directly examined using 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 7 days. Any colonies with the colonial appearance and typical caramel odor of *S. milleri* were subcultured to check for enhanced growth in carbon dioxide and were evaluated using the rapid strep system for species identification of streptococci (5). In brief, the rapid strep system consists of a strip with 20 capsules containing dehydrated substances for the determination of the following reactions; Voges-Proskauer; production of the enzymes pyrrolidony arylamidase, α-galactosidase, β-glucuronidase, β-galactosidase, alkaline phosphatase, leucine arylamidase; hydrolysis of esculin and hippurate; arginine dihydrolase; and fermentation of ribose, L-arabinose, mannitol, sorbitol, lactose, inulin, raffinose, starch, and glycogen. Viability plates were inoculated, incubated, and interpreted according to the instructions of the manufacturer. After incubation for 4 h, reagents were added to the Voges-Proskauer, hippurate, and enzyme wells, and results for all 20 reactions were recorded. A seven-digit profile number was generated and compared with those provided in a code book.

To classify the etiology of empyema, we isolated the pathogen from samples of pleural fluid and exudative pleural effusion, which satisfied Light's criteria (6) with predominant neutrophils. Causative microorganisms of pneumonia were otherwise defined as follows: (i) qualified sputum was obtained (presence of >25 leukocytes and <10 squamous cells per low-power magnification field [×10]), (ii) isolation of the probable pathogen when there was heavy growth ($\geqq 10^7$ CFU/ml) on quantitative culture.

Clinical characteristics of cases of empyema were compared by unpaired Student's *t* test. A value of $P < 0.05$ was considered significant.

Empyema was confirmed in 126 cases during the past 8 years. Empyema caused by *S. milleri* group was identified in 15 of these cases (12%). The clinical characteristics of cases showing empyema caused by the *S. milleri* group are shown in Table 1. The mean patient age was 62 years (range, 36-83) and 13 of 15 cases (87%) were male. Pneumonia was associated with the development of empyema in six cases (40%). Thirteen cases (87%) were cigarette smokers, and three (20%) had a history of excessive alcohol intake. Most patients (93%) demonstrated an underlying disease. Dental caries were noted in six cases, chronic obstructive pulmonary disease (COPD) in four cases, and diabetes mellitus in three cases. One case (7%) was taking oral corticosteroids, and six cases (40%) had previously received antibiotic treatment before admission.

The most common clinical symptoms at presentation were fever (93%), chest pain (93%), shortness of breath (60%), and cough (67%). A small percentage of patients had experienced hemoptysis (7%).

Concerning laboratory findings on admission, the leukocyte count and neutrophil count were elevated in all cases. Five cases (33%) showed renal dysfunction on admission, and eight cases (53%) showed hypoalbuminemia. Hypoxia (oxygen concentration below 60 mmHg in arterial blood) was recognized in six cases (40%). The findings of pleural fluid were exudative according to Light's criteria (6), and remarkable leukocytopenia with neutrophilia was noted in all cases.

*Corresponding author: Mailing address: Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan. Tel: +81-86-462-1111, Fax: +81-86-464-1041, E-mail: yoshihiro@med.kawasaki-m.ac.jp

Table 1. Clinical characteristics of 15 cases of empyema caused by *S. milleri* group

Variable	Empyema (n = 15)
Background	
Age (Mean ± SD)	36 - 83 (62.0 ± 10.4)
Gender (Male/Female)	13/2
Underlying disease	14 (93%)
Dental caries	6 (40%)
Chronic obstructive pulmonary disease	4 (27%)
Diabetes mellitus	3 (20%)
Others	7 (47%)
Clinical symptoms	
Fever (37.0°C≦)	14 (93%)
Chest pain	14 (93%)
Cough	10 (67%)
Treatment	
Antimicrobial treatment	15 (100%)
Carbapenem + Lincomycin	6 (40%)
Carbapenem	4 (27%)
Penicillin	3 (20%)
Cephem + Lincomycin	2 (13%)
Surgical treatment	
Chest drainage insertion	13 (87%)
VATS	6 (40%)
Prognosis	
Duration of hospitalization (Mean ± SD)	14 - 30 (19.6 ± 5.0)
Clinical effect	
Good	14 (93%)
Poor	1 (7%)
Recurrence	0
Mortality rate	1 (7%)

VATS, video-assisted thoracoscopic surgery.

Chest radiograph or computed tomography (CT) on admission showed loculation in 10 of the empyema cases (67%); eight were demonstrated in the left thoracic space, as were six pneumonias (40%). None of the cases was complicated by pneumothorax.

Regarding microbiological findings, *S. milleri* group was grown from pleural fluid in all cases (*S. constellatus* in nine, *S. intermedius* in five, and *S. anginosus* in one). Polymicrobial infection of the pleural space was identified in four cases (27%). Co-infecting bacteria were anaerobic in two cases, *Staphylococus aureus* in one and *Klebsiella pneumoniae* in one. Causative microorganisms were identified from sputum culture in five cases (33%). These five cases were concordant with the results of pleural fluid culture. *S. milleri* group was grown from sputum culture in three cases. None was grown from blood culture. All *S. milleri* group isolates were sensitive to penicillin or other common antibiotics.

As for treatment, all cases received various kinds of antibiotics during empiric treatment immediately after admission and continuing for a mean of 14.0 days (range 8 - 20): carbapenem and lincomycin in six cases, carbapenem in four, penicillin in three, and cephem and lincomycin in two. We considered that chest tube drainage was indicated when we judged that antibiotic treatment alone was not effective 3 - 5 days after admission. Thirteen cases (87%) were managed by both antibiotics and intercostal tube drainage for a mean of 8.4 days (range 5 - 18) and intrapleural streptokinase was administered through the chest tube in six cases (40%) in this series. Finally, six cases (40%) subsequently required decortication by video-assisted thoracoscopic surgery (VATS) a mean of 14.2 days (range 9 - 18) after the initiation of antibiotic treatment.

The median duration of hospitalization for all cases was 19.6 days (range 14 - 30). None of the patients was admitted to the intensive care unit. The clinical effect of antimicrobial treatment and/or surgical treatment was good in 14 cases (93%). However, there was no significant difference in clinical efficacy or prognosis between chest tube drainage and VATS drainage, because most of the cases of empyema responded well to surgical treatment. There was no recurrence of empyema. Only one case (7%) died of underlying disease (lung cancer), but death was not directly attributed to empyema by *S. milleri* in that case.

Predisposing factors that have been associated with *S. milleri* group empyema include mucosal disturbance (sinusitis, periodontal disease, enteric disease), preceding pneumonia, thoracic surgery, malignancy, neurological disease, alcohol abuse, and diabetes mellitus (7,8). In previously reported series of empyema, the most common predisposing factor was pneumonia, the average duration of hospitalization ranged from 12 to 56 days, and mortality ranged from 0 to 51% (9). In our series, predisposing factors were present in 93% of cases, the most frequent being pneumonia, which occurred in 40% of empyema cases, and dental caries, which also occurred in 40% of empyema cases.

S. milleri group reaches the thoracic space by several routes: (i) aspiration of oral secretions, (ii) direct implantation by trauma or surgery, (iii) extension by contiguity, and (iv) hematogeneous dissemination (7). Among these routes, two patterns were suspected in our series: hematogenous dissemination in 4 of 15 cases demonstrating dental caries but not pneumonia, and aspiration of oral secretion or extension by contiguity in 6 of 15 cases complicated by pneumonia. In some of our cases we suspected direct implantation by trauma or surgery had occurred, because there were no prior events.

While monomicrobial infection occurs in 30 - 83% of cases with *S. milleri* group thoracic infection, polymicrobial infection with anaerobes occurs in 17 - 60% (10-13). In our cases, *S. milleri* group was isolated in mixed pleural fluid culture with anaerobes in 13% of cases. These anaerobic microorganisms, which include *Peptostreptococcus* sp. and *Fusobacterium* sp., are common bacteria in the oral flora, and their presence in association with *S. milleri* group infection suggests an oropharyngeal source of infection. These bacteria may also play a role in promoting *S. milleri* group infection by delaying clearance, enhancing growth, and inhibiting bacterial activity of neutrophils (14). Although the pathogenic mechanisms involved in *S. milleri* group infections have not yet been fully elucidated, *S. milleri* group is known in some isolates to produce enzymes such as hyaluronidase, collagenase, and an immunosuppressant substance (15,16). Anaerobic microorganisms may also produce extracellular enzymes, and it has been proposed that these could act in concert with enzymes produced by the *S. milleri* group in causing tissue damage and spread of infection (14). In contrast to other reports in which the polymicrobial origin of the thoracic infection was associated with gastrointestinal origin and gastropleural fistula (17,18), this study demonstrated that polymicrobial infection was associated with respiratory origin, because flora commonly isolated from the respiratory tract such as anaerobic bacteria, *S. aureus* and *K. pneumoniae*, were isolated from the pleural fluid specimens of patients

with empyema.

Regarding the treatment of cases with empyema caused by *S. milleri* group, the need for combined treatments comprised of antibiotics and surgery was apparent in our series as well as in patients described in previous reports (11,19,20). Considering that many patients with empyema had dental caries as an underlying disease in this series, it is important to be aware that a careful examination of the mouth and teeth should be performed for patients with empyema caused by *S. milleri* group. Even when the appropriate antimicrobial chemotherapy is administered to patients with empyema caused by *S. milleri* group, it is not actually effective to treat empyema in these cases using only antibiotics such as intravenous penicillin, because transfer of antibiotics into the pleural space through loculated empyema is poor.

We could not identify any reasons for treatment failure in antimicrobial chemotherapy, such as inadequate dose, intervals of administration, or inappropriate antimicrobial agents through this study. In our series, 13 cases (87%) required surgical treatment involving chest tube insertion or VATS for decortication with antibiotics treatment. Porta et al. demonstrated that 75% of cases with *S. milleri* thoracic infection required surgical intervention (10). There has been increased interest in the use of intrapleural streptokinase to facilitate drainage and, with the development of purer formulations, this appears to be safe and effective (21,22). This form of treatment may be particularly suitable for empyema caused by *S. milleri* group because of the frequent occurrence of loculation. We also performed intrapleural streptokinase administration for six patients in this series. We consider it useful to facilitate drainage by resolving pleural loculation, which also shortens the duration of chest drainage tube insertion. Although the optimal method and timing of intervention for thoracic empyema remains controversial, patients are more likely to undergo successful VATS if the decision to intervene is not delayed. We have recently used VATS to obtain effective decortication as soon as possible when loculation of the intrapleural space due to empyema was complicated on thoracic echography.

REFERENCES

1. Whiley, R.A., Beighton, D., Winstanley, T.G., et al. (1992): *Streptococcus intermedius*, *Streptococcus constellatus*, and *Streptococcus anginosus* (the *Streptococcus milleri* group): association with different body sites and clinical infections. J. Clin. Microbiol., 30, 243-244.
2. Stelzmueller, I., Biebl, M., Berger, N., et al. (2007): Relevance of group Milleri Streptococci in thoracic surgery: a clinical update. Am. Surg., 73, 492-497.
3. Ripley, R.T., Cothren, C.C., Moore, E.E., et al. (2006): *Streptococcus milleri* infections of the pleural space: operative management predominates. Am. J. Surg., 192, 817-821.
4. Ahmed, R.A., Marrie, T.J. and Huang, J.Q. (2006): Thoracic empyema in patients with community-acquired pneumonia. Am. J. Med., 119, 877-883.
5. Appelbaum, P.C., Chaurushiya, P.S., Jacobs, M.R., et al. (1984): Evaluation of the rapid strep system for species identification of streptococci. J. Clin. Microbiol., 19, 588-591.
6. Light, R.W., MacGregor, M.I., Luchsinger, P.C., et al. (1972): Pleural effusions: the diagnostic separation of transdates and exudates. Ann. Intern. Med., 77, 507-513.
7. Hocken, D.B. and Dussek, J.E. (1985): *Streptococcus milleri* as a cause of pleural empyema. Thorax, 40, 626-628.
8. Shinzato, T., Uema, H., Inadome, J., et al. (1993): Bacteriological and clinical studies in 23 cases of thoracic empyema: the role of oral streptococci and anaerobes. Nippon Kyoubu Shikkan Gakkai Zasshi, 31, 486-491 (in Japanese).
9. Strange, C. and Sahn, S.A. (1991): Management of parapneumonic effusions and empyema. Infect. Dis. Clin. North Am., 5, 539-559.
10. Porta, G., Rodriguez-Carballeira, M., Gomez, L., et al. (1988): Thoracic infection caused by *Streptococcus milleri*. Eur. Respir. J., 12, 357-362.
11. Wong, C.A., Donald, F. and Macfarlane, J.T. (1995): *Streptococcus milleri* pulmonary disease: a review and clinical description of 25 patients. Thorax, 50, 1093-1096.
12. Morina, J.M., Leport, C., Cure, A., et al. (1991): Clinical and bacterial features of infections caused by *Streptococcus milleri*. Scand. J. Infect. Dis., 23, 659-666.
13. Shinzato, T. and Saito, A. (1995): The *Streptococcus milleri* group as a cause of pulmonary infections. Clin. Infect. Dis., 21(Suppl. 3), 238-243.
14. Shinzato, T. and Saito, A. (1994): A mechanism of pathogenicity of "*Streptococcus milleri*" group in pulmonary infection: synergy with an anaerobe. J. Med. Microbiol., 40, 118-123.
15. Unsworth, P.F. (1989): Hyaluronidase production in *Streptococccus milleri* in relation to infection. J. Clin. Pathol., 42, 506-510.
16. Ruoff, K.I. and Ferraro, M.J. (1987): Hydrolytic enzymes of "*Streptococcus milleri*". J. Clin. Microbiol., 25, 1645-1647.
17. Waitkins, D.B. and Dussek, J.E. (1985): *Streptococcus milleri* found in pulmonary empyema and abscess. J. Clin. Pathol., 38, 716-717.
18. Shlaes, D.M., Lerner, P.I., Wolinsky, E., et al. (1981): Infections due to Lancefield group F and related streptococci (*S. milleri*, *S. anginosus*). Medicine, 60, 197-207.
19. Moores, D.W.O. (1992): Management of acute empyema. Chest, 102, 1316-1317.
20. Tillotson, G.S. and Ganguli, L.A. (1984): Antibiotic susceptibilities of clinical strains of *Streptococcus milleri* and related streptococci. J. Antimicrob. Chemother., 14, 557-560.
21. Bouros, D., Schiza, S., Panagou, P., et al. (1994): Role of streptokinase in the treatment of acute locurated parapneumonic pleural effusions and empyema. Thorax, 49, 852-855.
22. Taylor, R.F.H., Rubens, M.B., Pearson, M.C., et al. (1994): Intrapleural streptokinase in the management of empyema. Thorax, 49, 856-859.