



Original Article

Case-control study of pneumonia patients with *Streptococcus anginosus* group bacteria in their sputum

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ARTICLE INFO

Article history:

Received 14 April 2016

Received in revised form

3 August 2016

Accepted 19 August 2016

Available online 25 September 2016

Keywords:

Streptococcus anginosus

Streptococcus intermedius

Streptococcus constellatus

Aspiration

Aspiration pneumonia

Nursing and healthcare-associated pneumonia

ABSTRACT

Background and objective: In recent years, *Streptococcus anginosus* group (SAG) bacteria are becoming increasingly recognized as important pneumonia-causing pathogens. Although several small studies have been reported, the features of SAG pneumonia remain unclear, because the identification of SAG from sputum cultures is not routinely performed in most microbiology laboratories. The aim of this study was to elucidate the clinical characteristics of SAG pneumonia.

Patient and methods: This was a retrospective case-control study utilizing data obtained in our hospital between September 2009 and June 2016. We investigated 31 patients with SAG pneumonia (PWP), and also assessed the difference between the 31 PWP and 37 patients without pneumonia (PWOP) in whose sputum SAG was detected.

Results: Seventy-one percent of the patients were men and the median age was 78 years in the PWP. Univariate analysis indicated that the PWP were significantly more often a bed-ridden ($p < 0.01$) with comorbid aspiration than were the PWOP ($p < 0.05$). Among the PWP, nursing and healthcare-associated pneumonia (NHCAP) was the more common type of pneumonia (54.8%). *S. anginosus* was detected significantly more frequently in sputum cultures of PWP than PWOP ($p < 0.01$), and multiple pathogens were detected more frequently in PWP ($p < 0.01$). *Streptococcus constellatus* was the most frequently detected pathogen in patients with a single bacterial infection. Empyema was observed only in patients with multiple bacteria.

Conclusions: SAG should be recognized as important causative pathogens of pneumonia, particularly among elderly patients with underlying disease associated with aspiration. NHCAP was the more common type of SAG pneumonia in this study.

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1. Introduction

The *Streptococcus anginosus* group (SAG), which includes *S. anginosus* (*S. anginosus*), *Streptococcus intermedius* (*S. intermedius*), and *Streptococcus constellatus* (*S. constellatus*), is generally known to

cause invasive pyogenic infections, such as empyema and abscess [1,2]. Moreover, SAG have a highly pathogenic nature; *S. intermedius* produces a leukocidin-like intermedilysin, whereas *S. anginosus* and *S. constellatus* display other toxins that exert a leukocidin-like effect associated with refractory infectious disease [3,4].

Although SAG was previously considered to rarely cause pneumonia, they have been recently found to be causative bacteria of pneumonia, particularly among elderly individuals [5–9]. In fact, 3–15% of cases of community-acquired pneumonia (CAP) were reportedly caused by SAG [10,11]. Thus, SAG pneumonia is not as rare as previously believed. Accordingly, the identification of SAG in

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routine cultures of sputum is a current policy at our institution. However, since SAG are resident members of the normal flora in the oral cavity and upper respiratory tract, the identification of SAG from sputum culture is not routinely performed in most microbiology laboratories. Moreover, it is often difficult to evaluate whether SAG bacteria are causative pathogens of pneumonia in clinical practice because SAG bacteria are not easy to grow on ordinary aerobic culture media [12]. Therefore, it is likely that conventional culture methods might overlook the pathogenicity of SAG and underestimate the epidemiology of pneumonia due to SAG. In addition, SAG is predictably susceptible to penicillin [13–15], and hence, their identification is generally considered unnecessary for patient management. Thus, the data regarding the clinical characteristics of patients with SAG pneumonia (PWP) is limited, and only a few studies have described the radiographic features of PWP [16].

The aims of this study were to assess the clinical characteristics and to compare the clinical features between PWP and patients without pneumonia (PWOP) in whose sputum SAG was detected. We also investigated the radiologic features of SAG pneumonia.

2. Methods

2.1. Study design and patient population

In this retrospective study, we enrolled PWP who were hospitalized at the Aichi Medical University Hospital between September 2009 and June 2016. PWP were classified as having CAP, nursing and healthcare-associated pneumonia (NHCAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). In addition, we evaluated the clinical manifestation of PWP, and compared the baseline characteristics between PWP and PWOP.

2.2. Definitions of pneumonia

All PWP exhibited new areas of infiltration on high-resolution computed tomography (HRCT) and newly presented with at least 2 of the following clinical findings: fever, coughing, sputum production, elevated white blood cell counts ($>8000/\mu\text{l}$), and elevated C-reactive protein levels ($>0.3\text{ mg/dl}$). Aspiration pneumonia was defined as patients with both risk factors for aspiration and evidence of gravity-dependent opacity on chest HRCT findings [17].

2.3. Data collection

All data were collected retrospectively from the database of the microbiology laboratory and patient medical charts. The acquired data included patient backgrounds, and bacteriological and radiological findings. Performance status was evaluated according to the European Cooperative Oncology Group [18].

2.4. Microbiological evaluation

In this study, we included purulent sputum samples with grade P1, P2, and P3 classified by Miller and Jones, and only selected sputum samples with bacterial phagocytosis by neutrophils. For SAG bacteria detection, sputum specimens were cultured on sheep blood agar (SBA) and incubated at $37\text{ }^\circ\text{C}$ in $5\% \text{CO}_2$ for 24–48 h, as described previously [8]. When typical colonies of SAG bacteria were observed, including a caramel odor and hemolysis in cultures, the representative colonies were sub-cultured onto SBA and re-incubated for 24 h in $5\% \text{CO}_2$. The phenotypic identification of isolates and antibiotic susceptibility testing was performed by RAISUS ANY (Nissui Pharmaceutical, Tokyo, Japan). Bacterial content was recorded as 1+ (equivalent to 10^3 – 10^5 colony-forming

units [CFU/mL]), 2+ (equivalent to 10^6 CFU/mL), or 3+ (equivalent to 10^7 CFU/mL).

2.5. Definition of terms

HAP was defined as pneumonia that occurred ≥ 48 h after hospitalization. CAP was classified as an acute type of pneumonia wherein the patient acquired the infection in the community [19], whereas NHCAP was considered in patients who met the following criteria [20]: residence in a nursing home or an extended-care ward; discharge from a hospital in the preceding 90 days; an elderly or handicapped patient who requires long-term care; or out-patients who regularly receive infusion therapy (chronic dialysis, antibiotics, cancer chemotherapy, or immunosuppressive drugs). VAP was defined when pneumonia was associated with mechanical ventilation.

2.6. Evaluation of radiologic findings

Two observers (a radiologist and a respiratory physician) assessed the presence of pneumonia and identified the opacity pattern of the pneumonia on chest HRCT scans.

2.7. Statistical analysis

To compare between the PWP and PWOP groups, we used the χ^2 or Fisher exact test for categorical variables and Student's t-test for continuous variables. The level of statistical significance was set at $p = 0.05$. All data were analyzed and processed using JMP[®] 8 (SAS Institute Japan).

2.8. Ethics

This case-control study was approved by the Human and Animal Ethics Review Committee of Aichi Medical University Hospital, Nagakute, Japan (approval number is 2015-H351).

3. Results

3.1. Clinical characteristics of the patients

During the study period, 68 patients were found to have SAG bacteria in the sputum, including 31 PWP and 37 PWOP. No other infections, such as endocarditis, intra-abdominal infection, or bone and soft tissue infection, were observed in PWP. The baseline characteristics of the PWP are shown in Table 1. Most patients were diagnosed as having aspiration pneumonia (28 of 31; 90.3%) and were more likely to be bed-ridden (26 of 31; 83.9%). Twenty of 31 patients were men (71%) and the median age, BMI, and serum albumin level were 78 years old, 19.7 kg/m^2 , and 3 mg/dL . Seven patients were classified as having CAP (22.6%), 17 had NHCAP (54.8%), 7 had HAP (22.6%) and none had VAP.

The distribution of inclusion criteria for NHCAP among the patients is described in Table 2. All patients with NHCAP met the criterion of “an elderly or handicapped patient who requires long-term care”.

Table 3 shows the comparison between PWP and PWOP. PWP had a significantly poorer PS level ($p < 0.0001$) and specific comorbid conditions, including cerebrovascular disease ($p = 0.0006$) and dementia ($p = 0.0195$), than did the PWOP. Bronchiectasis was more frequent in PWOP than in PWP ($p = 0.0854$). The PWOP also more often had underlying diseases of the lung, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, and interstitial pneumonia ($p = 0.0587$).

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