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Case report

Pleural empyema and streptococcal toxic shock syndrome due to *Streptococcus pyogenes* in a healthy Spanish traveler in Japan

Tetsuya Sakai[a,*], Daisuke Taniyama[b], Saeko Takahashi[a], Morio Nakamura[a], Takashi Takahashi[c,**]

[a] Department of Respiratory Medicine, Tokyo Saiseikai Central Hospital, 1-4-17 Mita, Minato-ku, Tokyo 108-0073, Japan
[b] Department of General Internal Medicine, Tokyo Saiseikai Central Hospital, 1-4-17 Mita, Minato-ku, Tokyo 108-0073, Japan
[c] Laboratory of Infectious Diseases, Kitasato Institute for Life Sciences & Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

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ABSTRACT

Group A *Streptococcus* (GAS, *Streptococcus pyogenes*) causes invasive infections including streptococcal toxic shock syndrome (STSS) and local infections. To our knowledge, this is the first report of a case of an invasive GAS infection with pneumonia and pleural empyema (PE) followed by STSS (disseminated intravascular coagulation [DIC] and acute renal insufficiency) in a healthy male adult. He received combined supportive therapies of PE drainage, anti-DIC agent, hemodialysis, and antimicrobials and eventually made a clinical recovery. GAS isolated from PE was found to have *emm1/speA* genes, suggestive of a pathogenic strain. Clinicians should be aware of the possibility of this disease entity (pneumonia, PE, and STSS) in healthy male adults as well as children and adult women.

Introduction

β-hemolytic Lancefield group A *Streptococcus* (GAS, *Streptococcus pyogenes*) is a well-known causative pathogen of upper respiratory tract and cutaneous infections and occasionally leads to streptococcal toxic shock syndrome (STSS). Although GAS is an uncommon pathogen of community-acquired pneumonia (CAP), its clinical course is fulminant and it comprises approximately 25% of CAP cases accompanied by STSS [1]. However, GAS is rarely isolated from pleural empyema (PE). We herein report a severe invasive GAS infection including CAP and PE followed by STSS with acral desquamation at peripheral sites of the hand and foot as typical manifestation of GAS STSS in a healthy Spanish traveler in Japan.

Case report

A 32-year-old, previously healthy man was admitted to our hospital with fever, cough, severe back pain, and oliguria. The patient was a Spanish tourist who worked in England and came to Japan 8 days before visiting our hospital. Four days before hospital admission, he had a cough and fever and developed oliguria 2 days before the visit.

On admission to the emergency room, the patient was afebrile, but he exhibited a blood pressure of 96/57 mmHg, respiratory rate of 40 breaths/min, and oxygen saturation of 90% while breathing under an oxygen mask (15 L/min). Chest respiratory rales were heard over the right middle and lower lung fields. Physical examinations were otherwise normal. His leukocyte cell count and C-reactive protein concentration were 3300/μL and 49.9 mg/dL, respectively. Serum levels of urea nitrogen, creatinine, and fibrinogen degradation products were 69 mg/dL, 5.4 mg/dL, and 40.3 μg/mL, respectively. Chest radiography revealed a poor lucent image of the whole right lung. Contrast-enhanced chest computed tomography showed a consolidation on the right upper and middle lobes including a large amount of right pleural effusion with pleural thickening. Thoracocentesis was performed, and cloudy yellowish pus was aspirated (Fig. 1), which was sent for bacterial culture along with two sets of blood cultures. Gram staining of the PE culture showed numerous Gram-positive cocci with many leukocytes.

Clinical diagnosis of sepsis with disseminated intravascular coagulation (DIC) and acute renal insufficiency due to CAP with PE was made based on these findings. A chest drainage tube was inserted, and intravenous administration of vancomycin and meropenem was initiated with the administration of an anti-DIC agent. Because of his acute renal insufficiency, hemodialysis was performed for 4 days. On hospital day 3, the PE culture revealed growth of GAS, while blood cultures were sterile. This isolate was stored at −80 °C until further evaluation. STTS

* Corresponding author.
** Corresponding author.
E-mail addresses: sakai.tetsuya.330@gmail.com (T. Sakai), taka2si@lisci.kitasato-u.ac.jp (T. Takahashi).

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Fig. 1. Aspirated (left side) and drainage (right side) pus from pleural empyema.

was subsequently diagnosed, and vancomycin and meropenem were replaced by combined intravenous administration of penicillin and clindamycin.

The patient eventually made a clinical recovery. The chest tube was removed on hospital day 8 and he was discharged on day 15. During hospitalization (on hospital day 9), acral desquamation erupted at peripheral sites of the hand and foot (Fig. 2**)**, which was considered as typical dermatologic manifestations of STSS.

Microbiological analyses

Phenotypic and genotypic features of the GAS isolate (named strain TA2) were determined and are summarized in Table 1. Phenotypic analyses included colonial morphology on sheep blood agar plate, identification percentage by numerical profile using the Rapid ID 32 Strep API system (SYSMEX bioMérieux Co., Ltd., Tokyo, Japan), and identification score value by matrix-assisted laser desorption/ionization-time of flight mass spectrometry using MALDI BioTyper™ (version 3.1) software (Bruker Daltonics GmbH, Leipzig, Germany). Antimicrobial susceptibility was determined using the broth microdilution method [2]. Genomic analyses compared the similarity (in%) of strain TA2 and type strain JCM 5674^T using 16S rRNA gene sequencing [3], and determined the *emm* type (subtype) with the full-length sequences [4], sequence type (ST) [5], *sic* allele [6], and macrolide/lincosamide (ML) resistance determinants, including *erm*(A), *erm*(B), and *mef*(A) [7]. We also examined the exotoxin gene profile (*speA-speB-speC-ssa-smeZ*) to assess the relationship between the profile and onset of STSS [8]. Briefly, all *emm* typing (sub-typing) was performed as described by the Centers for Disease Control and Prevention (http://www2a.cdc.gov/ncidod/biotech/strepblast.asp); full-length sequencing was performed with the same PCR primers. Multilocus sequence typing (MLST) to determine ST was performed by sequencing seven housekeeping genes (*gki*, *gtr*, *murI*, *mutS*, *recP*, *xpt*, and *yqiL*) according to the GAS pubMLST website (http://pubmlst.org/spyogenes/). The *sic* gene was amplified with primer pair SIC.1/SIC.2; sequencing was also performed with this primer pair. The *sic* allele number was determined and assigned by comparison to the reference allele. The three ML resistance genes and the five exotoxin genes (with 16S rRNA and *speB* as internal controls) were amplified by PCR and confirmed by the corresponding amplicon size on agarose gel electrophoresis. Genomic analyses revealed that the *emm* genotype/full-length sequence, ST, *sic* allele, exotoxin gene profile, and ML resistance determinant were *emm1*/identity similar to strain MGAS5005, ST28, *sic1.02*, *speA-speB-smeZ*, and *mef*(A), respectively.

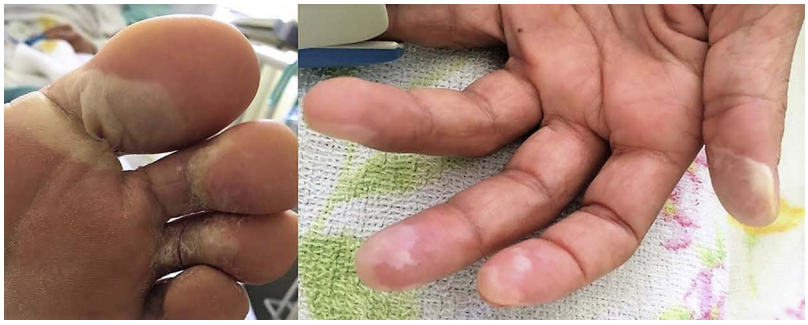

Fig. 2. Desquamation of the palms (right side) and soles (left side) on hospital day 9.

Table 1
Phenotypic and genotypic characteristics of *Streptococcus pyogenes* isolate from a Spanish traveler with pleural empyema. .

Phenotypic and genotypic parameters	Strain TA2
Clinical specimen	Pleural effusion
Gross appearance of colonies on sheep blood agar plate	Non-mucoid, beta-hemolytic small-size grey smooth colonies
Numerical profile using the Rapid ID 32 Strep API system (% probability)	54032161(98.1)
Identification score value by MALDI-TOF MS	2.457
Similarity (%) of *S. pyogenes* type strain[a] using 16S rRNA sequencing (reading size, bp)	100 (1422)
emm type (subtype)	*1* (.0)
emm full-length (reading size, bp)	Identical to that of *S. pyogenes* MGAS5005 strain[b] (1098)
Sequence type (allelic profile: *gki-gtr-murI-mutS-recP-xpt-yqiL*)	28 (4 – 3-4-4-4-2-4)
Streptococcal inhibitor of complement (*sic*) allele No. (reading size, bp)	*sic1.02* (956)
Amplified exotoxin genes	*speA-speB-smeZ*
Antimicrobial resistance agent[c]	Erythromycin and azithromycin
Macrolide resistance determinant	*mef*(A)
Antimicrobial agents	Minimum inhibitory concentration (μg/mL)
Penicillin G	≤0.03
Ampicillin	≤0.06
Amoxicillin/clavulanic acid	≤0.25
Cefotiam	≤0.5
Cefotaxime	≤0.12
Ceftriaxone	≤0.12
Cefepime	≤0.5
Cefozopran	≤0.12
Cefditoren pivoxil	≤0.06
Meropenem	≤0.12
Erythromycin	> 2
Azithromycin	> 4
Clindamycin	≤0.12
Minocycline	≤0.5
Chloramphenicol	≤4
Vancomycin	0.5
Levofloxacin	1
Sulfamethoxazole-trimethoprim	≤0.5

MALDI-TOF MS, matrix-assisted laser desorption ionization-time of flight mass spectrometry.

[a] *S. pyogenes* JCM 5674(T).

[b] Accession number is CP000017.2.

[c] Resistance to antimicrobials was determined by the broth microdilution method according to the Clinical and Laboratory Standards Institute document M100-S22.

Discussion

To the best of our knowledge, this is the first report describing an invasive GAS infection with CAP followed by PE that resulted in STSS in a healthy male adult.

Since the mid-1980s, concern has grown that invasive GAS infections have increased both in incidence and severity. Invasive soft tissue infections and bacteremia are common clinical manifestations, whereas pneumonia and STSS account for approximately 10% of such cases [9]. GAS is an uncommon cause of CAP, comprising < 1% of CAP [10]. This disease entity usually occurs as secondary pneumonia following other respiratory infections (e.g., influenza, pertussis, and measles) or in patients with chronic obstructive pulmonary diseases. Clinical characteristics of GAS CAP are sudden onset of fever, chills, dyspnea, productive cough, and pleuritic pain. The most characteristic feature is rapid accumulation of pleural effusion noted in up to 80% of cases, as compared to 10% of pneumonia by other causative agents [11]. However, the prevalence of GAS-associated PE is only 0.7% in patients with PE [12]. GAS isolation from pleural fluid was observed in only one case among 40 patients with GAS CAP [8]. However, approximately 50% of GAS CAP patients present with invasive infections, and 25% develop STSS, which has high mortality rates (estimated at 20–38%) [8,9]. Therefore, clinicians should be aware of this potential clinical manifestation (CAP, PE, and STSS) as invasive disease.

The GAS M protein is a major bacterial virulence factor that confers resistance to phagocytosis. Analysis of the *emm* gene, which encodes the amino acid sequence at the N-terminal end of M protein, is used in epidemiological studies to characterize outbreaks of GAS. Among 82 invasive GAS isolates from Japan, *emm1* was most prevalent (n = 27, 32.9%) and significantly related to poor outcomes (infection-associated sequelae or death) [13]. Further, a retrospective study of molecular features of these invasive strains showed a highly significant association of the presence of *speA* gene (encodes a streptococcal pyrogenic exotoxin [superantigen]) with the onset of STSS [14]. Of the 40 strains causing CAP, prevalent clones which caused the most severe cases were *emm1* (43.6%) and *speA* (51.3%). Compatible with these findings, strain TA2 in this case possessed *emm1/speA* genes, suggestive of a highly pathogenic strain. Yoshida et al. reported complete whole-genome sequences of mucoid and nonmucoid GAS strains (MTB313 and MTB314, accession numbers AP014572 and AP014585, respectively) simultaneously isolated from the cerebrospinal fluid of a patient with meningitis [15]. The *emm* genotype/full-length sequence, ST, *sic* allele, exotoxin gene profile, and ML resistance determinant of strain TA2 were identical to that of strains MTB313/MTB314. Therefore, these pathogenic strains seem to be circulating in local areas in Japan.

Desquamation of the palms and soles appears in approximately 20% of STSS cases and usually occurs several days after disease onset [16]. Pyrogenic exotoxins produced by certain GAS strains may be responsible for desquamation. The relationship between PE due to GAS and acral desquamation has been occasionally noted. Thus, this desquamation pattern might be a suggestive finding to identify GAS as the etiologic agent, particularly when culture results are inconclusive [17].

Conclusion

Clinicians should be aware of the possibility of CAP, PE, and STSS as an invasive GAS infection in healthy male adults, as well as children and adult women as previously described. We also recommend epidermolysis at peripheral sites of the hand and foot as typical manifestations of GAS STSS for clinicians.

Informed consent

The patient gave his informed consent before this article was written.

Conflict of interest

The authors have disclosed no relevant financial relationships.

Ethical approval

Ethical approval was not required for this study.

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