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Case Report

Whole genome analysis of a multidrug-resistant *Streptococcus pneumoniae* isolate from a patient with invasive pneumococcal infection developing disseminated intravascular coagulation

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ABSTRACT

Multidrug-resistant *Streptococcus pneumoniae* strains were isolated from blood and sputum of a patient with disseminated intravascular coagulation in Sapporo city, Japan. These antibiograms were only susceptible to vancomycin, linezolid, daptomycin, some carbapenems, and some fluoroquinolones. Identical antibiograms, serotypes (19F), and sequence types (ST10017) suggested a shared origin of these isolates. Only one ST10017 strain has been isolated in the same city in Japan previously (2014), and the 2014 isolate is still susceptible to macrolides. The whole genome of the blood-derived isolate was sequenced. The strain harbored resistance mutations in *parC*, *gyrA*, *pbp1a*, *pbp2a*, *pbp2b*, and *pbp2x*, and harbored the resistance genes, *ermB* and *tetM*. The nucleotide sequences of *parC* and *pbp2x* genes of strain MDRSPN001 were clearly different from those of other *S. pneumoniae* strains and were similar to those of oral streptococci strains. These findings suggest that strain MDRSPN001 has been rapidly and drastically evolving multidrug resistance by gene replacement and accumulation of genes originating from other strains, such as oral streptococci, *Streptococcus mitis*.

1. Introduction

Streptococcus pneumoniae is the most common etiological agent for community-acquired pneumonia especially in the elderly. This bacterium is also found among the nasopharyngeal flora during childhood and frequently causes acute otitis media and sinusitis. Furthermore, it may cause invasive infectious diseases, such as meningitis and sepsis [1–3]. Conjugated vaccines containing 13 (e.g., PCV13) or 10 serotype polysaccharides are approved for the prevention of invasive infections in children, especially meningitis. A polysaccharide vaccine containing 23 serotypes and PCV13 are used for the prevention of pneumonia and invasive infections in the elderly and immunocompromised hosts, such as those undergoing splenectomy [4–6].

Abbreviations: CHDF, continuous hemodiafiltration; CIP, ciprofloxacin; CLSI, Clinical Laboratory Standards Institute; ICU, intensive care unit; IVGG, intravenous γ-globulin; JANIS, Japan Nosocomial Infections Surveillance; MIC, minimum inhibitory concentration; PC, platelet concentrate; PCV, pneumococcal conjugated vaccine; PMX, polymyxin B-immobilized fiber column perfusion; PRSP/PISP, penicillin-resistant/intermediate *S. pneumoniae*; TM-α, thrombomodulin-α; TZP, tazobactam/piperacillin.

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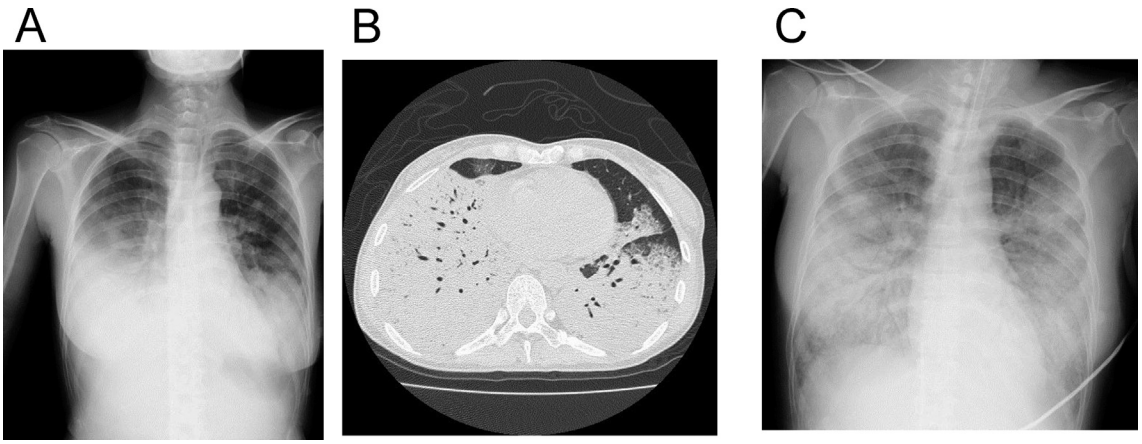

Fig. 1. X-ray radiography of the patient on Day5 (A) and Day 8 (C) of onset. Computed tomography of the patient on Day 5 of onset (B).

Antimicrobial resistance is a serious problem in the treatment of *S. pneumoniae* infections, and penicillin-resistant/intermediate *S. pneumoniae* (PRSP/PISP) is particularly problematic [7]. The rate of macrolide resistance among *S. pneumoniae* isolates is extremely high (more than 80%) in Japan and fluoroquinolone resistance has also been observed, albeit at a lower rate (ca. 3%) [8,9]. It is feared that multidrug-resistant *S. pneumoniae* strains will evolve and the treatment of their infections will become intractable.

Here, we report a case of a severe invasive *S. pneumoniae* infection with developing disseminated intravascular coagulation. The isolates derived from the sputum and blood were multidrug-resistant. The whole genome sequence of the blood-derived strain was determined as described previously [10]. This study was approved by the Institutional Review Board of the NTT East Sapporo Hospital.

2. Case report

2.1. Case presentation

A 58-year-old female (height, 153 cm; weight, 43 kg) declared no significant clinical history, no previous history of drinking, and a previous history of smoking (three cigarettes per Day). On Day 1 of onset, she reported a cough and sputum, on Day 2, fever, and Day 4, respiratory distress.

On Day 5, she was admitted to a hospital, and her peripheral capillary oxygen saturation (SpO_2) was 66% on admittance. The patient was then transferred to NTT East Sapporo Hospital and admitted to the intensive care unit (ICU). X-ray radiography revealed diffuse infiltrative shadows in both lungs (Fig. 1A), and computed tomography revealed an infiltration in the inferior and

Table 1
Vital signs and laboratory test finding of the patient.

Subject	Standard value	Value			
		Day 5	Day 6	Day 7	Day 8
Highest body temperature (°C)		38.0	39.6	39.4	35.5
Blood pressure (mmHg)		112/42	118/31	132/43	98/38
White blood cell count ($\times10^3$/μl)	3.2–7.0	1.4	3	26.8	33.7
Red blood cell count ($\times10^6$/μL)	3.70–4.90	3.74	3.38	3.03	2.66
Platelet ($\times10^4$/μL)	14.4–31.1	7.5	1.8	0.5	0.5
Hemoglobin (g/dL)	10.8–15.2	11.7	10.6	9.6	8.3
Hematocrit (%)	34.0–45.0	33.0	29.8	28.1	25.5
Fibrinogen (mg/dL)	180–330	768	-	-	-
Antithrombin III (%)	80–120	46	-	-	-
Fibrin/fibrinogen degradation products (μg/mL)	≤5	26.1	-	-	-
D-Dimer (μg/mL)	≤1	11.3	-	-	-
Total protein (g/dL)	6.4–8.0	4.6	3.4	3.6	3.2
Albumin (g/dL)	3.9–5.2	1.9	1.3	1.2	1.2
Total bilirubin (mg/dL)	0.3–1.3	0.6	0.5	0.7	2.2
Aspartate aminotransferase return (U/L)	13–33	56	62	155	21870
Alanine aminotransferase return (U/L)	8–46	18	11	30	3062
Lactate dehydrogenase (U/L)	125–219	321	395	795	33990
Alkaline phosphatase (U/L)	125–323	260	107	131	468
Urine nitrogen (mg/dL)	9–20	21	37	45	12
Creatinine (mg/dL)	0.50–0.80	0.67	1.79	2.62	1.28
Na (mmol/L)	137–144	140	141	135	135
K (mmol/L)	3.6–4.8	2.4	3.6	5.6	5.8
Cl (mmol/L)	101–108	105	108	101	102
C-reactive protein return (mg/dL)	<0.1	23.72	16.56	16.73	5.04
β-D-Glucan (pg/mL)	<11	<3	-	-	-
Endotoxin (pg/mL)	<5	-	-	45	-

-: not tested.

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