IDCases 36 (2024) e01936

Contents lists available at ScienceDirect

IDCases

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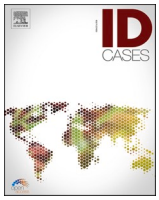

Case report

Invasive pneumococcal serotype 3 infection following pneumococcal vaccination in a hematopoietic stem cell transplant patient: A case report

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ARTICLE INFO

Keywords:
Hematopoietic stem cell transplant
PPSV23
PCV13
Invasive pneumococcal disease
Vaccination breakthrough
Serotype 3
Streptococcus pneumoniae

ABSTRACT

Given the high mortality rate of invasive pneumococcal disease (IPD) in hematopoietic stem cell transplant (HSCT) recipients, vaccination is recommended. These recipients respond to most vaccines; however, their immune response is typically weaker during the first months or years after transplantation, compared with that of healthy individuals. Here, we report a case of IPD with serotype 3 pneumonia and empyema in an HSCT recipient who had received three doses of the 13-valent pneumococcal conjugate vaccine (PCV) and one dose of the 23-valent pneumococcal polysaccharide vaccine; furthermore, the recipient had no relapse, graft-versus-host disease, or use of immunosuppressive agents after allogeneic HSCT for acute myeloid leukemia. Moreover, we discussed the characteristics of serotype 3 *Streptococcus pneumoniae*, a case series of breakthrough infections with *S. pneumoniae* in HSCT recipients who received pneumococcal vaccines, and the potential implications for the upcoming PCV15 and PCV20 vaccines for serotype 3.

Introduction

Invasive pneumococcal disease (IPD) occurs in approximately 6% of hematopoietic stem cell transplant (HSCT) recipients; therefore, pneumococcal vaccination is recommended [1]. The European Conference on Infections in Leukemia guideline recommends three doses of pneumococcal conjugate vaccine (PCV) one month apart, starting from 3 months after HSCT. Furthermore, a fourth dose of PCV or one dose of pneumococcal 23-valent polysaccharide vaccine (PPSV23) is recommended in case of graft-versus-host disease (GVHD) 6 months later [2]. However, PPSV23 has been ineffective in generating antibodies in HSCT recipients due to its low immunogenicity [3], and GVHD can reduce the response to vaccination [4]. There have been reports of breakthrough cases despite vaccination with pneumococcal vaccine [5,6]. We report a case of serotype 3 IPD in a patient with acute myeloid leukemia (AML) who received pneumococcal vaccinations four years post- HSCT and has not experienced an AML relapse or GVHD. Additionally, we discuss the characteristics of serotype 3 *Streptococcus pneumoniae*, a series of breakthrough infections with *S. pneumoniae* in HSCT recipients despite pneumococcal vaccination, and the potential implications for the new PCV15 and PCV20 vaccines in the context of serotype 3.

Case presentation

A 57 year-old male was experiencing a sore throat and cough for 1 month prior to admission. On the day before admission, the patient experienced fever, with a recorder temperature of 37.2 °C, with chills and visited our emergency department. His medical history was as follows: 14 years prior to admission, the patient underwent a right lower lobe resection for right lower lobe lung cancer and developed chronic unilateral pleural effusion. Ten years prior to admission, the patient received radiation therapy for right middle lobe lung cancer; four years before admission, the patient was administered with induction therapy for AML. Furthermore, in the same year, he was treated with a cord blood transplantation. The conditioning regimen was as follows: fludarabine 30 mg/m^2 for 6 days, IV busulfan 3.2 mg/kg for 4 days, melphalan 40 mg/m^2 for 2 days, and total body irradiation of 3 Gy. Neutrophil engraftment occurred within 14 days of the transplant. The patient's medical history revealed that he had received PCV13 vaccinations thrice, with the last vaccination administered 3 years prior to admission. This was followed by a PPSV23 vaccination 2 years prior to admission, due to the absence of chronic GVHD. The patient also has a history of suspicion of type IV allergy to piperacillin/tazobactam.

On arrival, the vital signs were as follows: conscious level, clear; body temperature, 39.8 °C; blood pressure, 124 mmHg/64 mmHg;

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https://doi.org/10.1016/j.idcr.2024.e01936
Received 14 September 2023; Received in revised form 31 January 2024; Accepted 31 March 2024
Available online 12 April 2024

respiratory rate, 18 breaths/min; and oxygen saturation, 95% (with 5 L/min oxygen). Laboratory tests revealed a white blood cell count of 27,700 cells/μL (stab 23.0%, seg 62.5%, lymphocyte 6%) and a C-reactive protein level of 10.7 mg/dL. Physical examination revealed decreased breath sounds in the right lung field. We conducted a pharyngeal swab, which was analyzed using FilmArray® Respiratory 2.1 Panel (BioMerieux, France); the result was positive for human coronavirus OC43 (HCoV-OC43). The urinary *Streptococcus pneumoniae* (*S. pneumoniae*) antigen test result was negative. Chest radiography revealed pleural effusion in the right lung field (Fig. 1A). Chest computed tomography (CT) revealed a known pleural effusion and a new consolidation in the right lower lobe (Fig. 2A), leading to a diagnosis of bacterial pneumonia and hospital admission. We suspected bacterial pneumonia with HCoV-OC43 infection. He was administered meropenem and azithromycin. Three hours after admission, due to worsening respiratory status with oxygen saturation dropping to 70% on 10 L/min oxygen, another the chest radiograph was obtained and revealed further consolidation of the right lung field (Fig. 1 B). Subsequently, the patient was transferred to the intensive care unit (ICU) and intubated. Penicillin-sensitive *S. pneumoniae* was detected in both the sputum and blood cultures, with colonies shown in Fig. 3 and antimicrobial susceptibility detailed in Table 1. He was diagnosed with IPD. Due to the suspicion of a type IV allergy to piperacillin/tazobactam and possible cross-reactivity, we could not use penicillin G. Therefore, he was treated with the antibiotic ceftriaxone. Subsequently, the patient's respiratory status improved and was extubated on day 7 of hospitalization; he was then transferred from the ICU. However, due to persistent fever, a chest CT was performed on day 8 of hospitalization, which revealed an encapsulated pleural effusion in the right lung field (Fig. 2B). Thoracentesis was performed and the fluid appeared clear. The cell count of the pleural effusion was 5677/μL with neutrophils comprising 99.0% of these cells. The total protein and albumin levels were 3.0 g/dL and 1.6 g/dL, respectively. The lactate dehydrogenase (LDH) level was notably high at 2276 U/L. The glucose level was less than 2 mg/dL and the pH was 7.0. In the serum, the total protein and albumin levels were 5.2 g/dL and 1.8 g/dL, respectively. The serum LDH level was 136 U/L. Although the pleural fluid culture was negative, we suspected the presence of empyema due to low glucose levels and elevated blood cell count with neutrophil predominance.

On day 11 of hospitalization, chest tube drainage was performed, which resulted in a decrease in the pleural effusion (Fig. 4), and the patient's condition subsequently subsided and stabilized. In both the sputum and blood culture, *S. pneumoniae* serotype 3 was identified by the Tokyo Metropolitan Institute of Public Health.

Discussion

Herein, we report a case of serotype 3 IPD with pneumonia co-infected with human coronavirus OC43 and empyema in the HSCT recipients who had received three doses of PCV13 and one dose of PPSV23 and without history of AML relapse or GVHD. We have discussed the potential reasons for the breakthrough infection in an HSCT recipient with multiple pneumococcal vaccinations and the characteristics of *S. pneumoniae* serotype 3.

This case involved IPD associated with HCoV-OC43. It is recognized that co-infection with COVID-19 and pneumococcal pneumonia can occur, as documented in case series [5]. Additionally, a study in children suggests that, although uncommon, co-infection with human endemic coronavirus and pneumococcus is possible [5]. Therefore, it is advisable to consider submitting pneumococcal urinary antigen and sputum culture when respiratory viral infection coexisting with pneumococcal pneumonia is suspected.

Hematopoietic stem cell transplant recipients typically have low levels of specific antibodies, particularly immunoglobulin (Ig) G2 and IgG4, and reduced serum opsonophagocytic activity [7]. Moreover, allogeneic HSCT recipients commonly respond poorly to PPSV23. However, when administered 12–18 months after the administration of three doses of PCV7, PPSV23 has been shown to elicit a response in more than 80% of patients, including 42% of those who did not respond to PCV7 [8].

However, breakthrough cases despite pneumococcal vaccination have been reported. Youssef et al. studied 7888 HSCT patients, and identified 47 cases of pneumococcal infection, resulting in 6 deaths, and 5 cases of breakthrough infection despite prior vaccination with a conjugate pneumococcal vaccine [9]. The median time of pneumococcal disease was 546 ± 732 days after vaccination. The study did not report the specific contents of the conjugate vaccine or the serotypes of the breakthrough infections. Kumar et al. also examined HSCT recipients, and 14 cases of breakthrough infections were observed, with serotyping available for 13 of these cases [10]. The most frequent serotypes were 23 F (3 of 13, 23.1%), 6B (3 of 13, 23.1%), and 9 V (2 of 13, 15.4%). The remaining patients had one of the following serotypes: 4, 7 F, 18 C, 19 A, and 22 F, but serotype 3 was not identified in any of the cases. Three of these patients have received the PPSV23 vaccine. Furthermore,

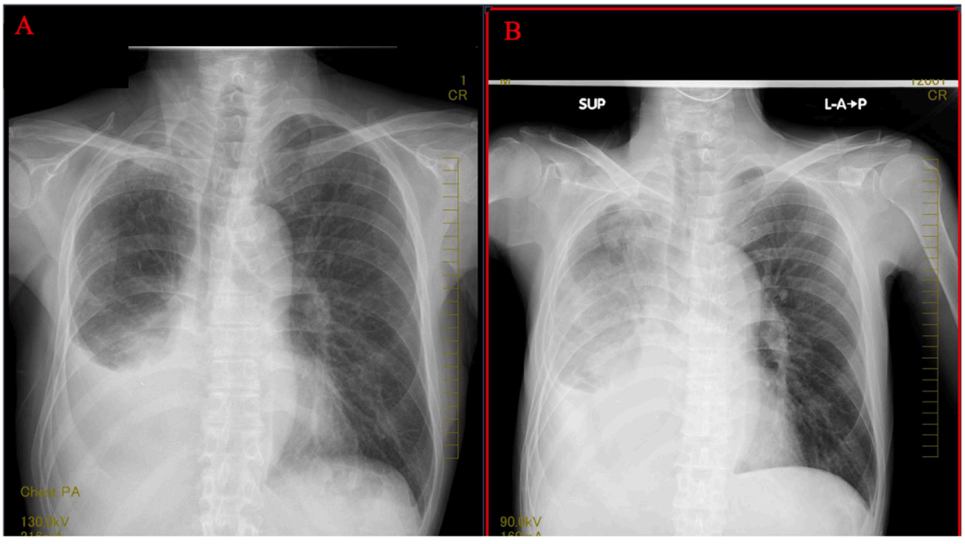

Fig. 1. Chest radiography. (A) Chest radiography on admission shows pleural effusion in the right lower lung field; (B) the one performed on admission to the ICU, shows consolidation throughout the right lung field. Abbreviation: ICU, intensive care unit; CT, computed tomography.

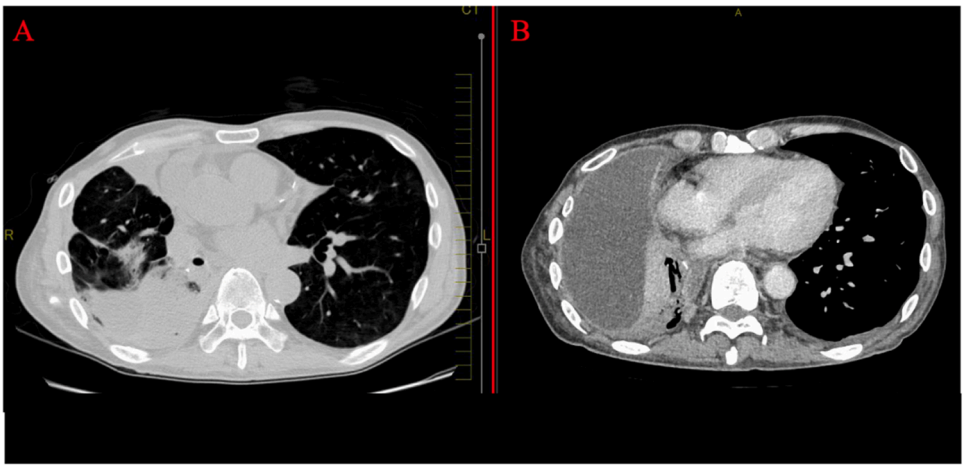

Fig. 2. Chest CT. (A) Chest CT performed on admission (lung windowing) shows a slight infiltration shadow and pleural effusion in the lower right lobe. (B) Chest CT performed on day 8 (mediastinal windowing with contrast) shows an encapsulated pleural effusion. Abbreviation: ICU, intensive care unit; CT, computed tomography.

Fig. 3. Mucoid type of *Streptococcus pneumoniae* colony on blood agar.

Table 1
Pleural effusion and blood test findings at drainage.

	Pleural effusion	Serum
Cell count (/μL)	5677 (neutrophil 99.0%)	
Appearance	Clear	
Total protein (g/dL)	3.0	5.2
Albumin (g/dL)	1.6	1.8
LDH (U/L)	2276	136
Glucose (mg/dL)	< 2	
pH	7.0	

IPD occurred at a mean of 10.5 ± 9.4 months (range 0.5–19.1 months) post vaccination. In another study by Okinaka et al., pneumococcal infections in allogeneic HSCT recipients occurred as a delayed-onset condition, at 1 year or more after the transplantation [11]. Therefore, patients who have undergone HSCT and received pneumococcal vaccination should be carefully monitored for late-onset breakthrough infections.

Pneumococcal serotype 3 infections are characterized by severe clinical symptoms such as empyema, bacteremia, endocarditis, and meningitis, with a mortality rate of 30–47% [12]. Clinical isolates that produce serotype 3 capsule have a mucoid appearance on the plates [12] and exhibit a wet phenotype that is distinct from that of many other pneumococcal isolates. The colonies in the culture of our patient's sample also exhibited similar characteristics. Although serotype 3 is included in both PPSV23 and PCV13, reports indicated that the incidence of serotype 3 IPD did not change significantly before or after the introduction of these vaccines [13]. Serotype 3 pneumococci were frequently detected in Japanese individuals aged 65 years or older [12, 13].

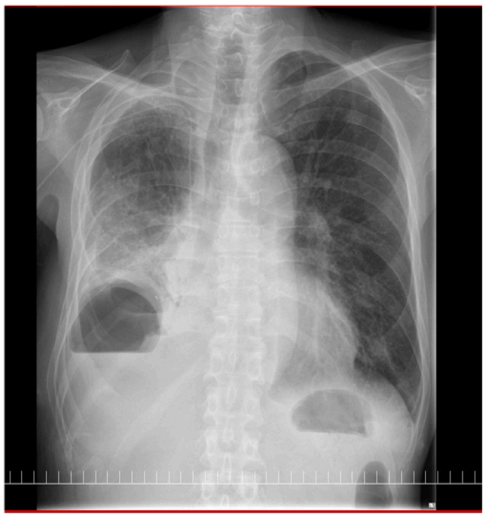

Fig. 4. Chest radiography after drainage. Chest radiography after drainage shows that the right pleural effusion decreased. An air-fluid level (a "niveau") appears because the patient had undergone a lower lobectomy.

Miyazaki et al. [14] proposed two possible reasons for the ineffectiveness of PCV13 against serotype 3. First, vaccine components targeting serotype 3 generate only weak immunogenicity. Second, the polysaccharides comprising the serotype 3 capsule can be shed from the surface of pneumococcal bacteria, rendering it difficult for antibodies to effectively kill these bacteria. Randomized controlled trials comparing PCV13 with PCV7 have shown that the newly identified nasopharyngeal acquisition of serotype 3 does not change with the introduction of PCV13 [15]. Regarding PPSV23, data on the association with serotype 3 are limited. However, existing reports indicate that some immunocompetent patients do not achieve sufficient immunity against serotype 3, even after receiving PPSV23 [16]. In another prospective cohort study aimed at increasing the number of responders, HSCT recipients received four doses of the PCV13 and one dose of PPSV23 starting 4–6 months after HSCT, serotype-specific IgG level to serotypes 3 was ineffective [17]. Therefore, caution should be exercised when breakthrough serotype 3 infections are present.

Streptococcus pneumoniae infection occurs in HSCT patients, as they have lower immunogenicity against serotype 3 and may have a higher risk of complications such as the development of empyema.

This study has some limitations. As serum type antibodies to the *S. pnueumoniae* in this patients were not followed up after vaccination, it is uncertain whether or not the HSCT recipient responded to the pneumococcal vaccine or if the nature of pneumococcal serotype 3 led to a breakthrough despite pneumococcal vaccination.

As a future prevention strategy for pneumococcal infection, the PCV15 vaccine contains the 13 serotypes included in the PCV13 and 2 additional serotypes (22 F and 33 F). In phase III trials, PCV15 showed equivalent coverage to PCV13 for common serotypes, and geometric mean titers (GMT) for serotype 3 were superior to those of PCV13 [18]. Another option is PCV20 that contains serotypes 8, 10 A, 11 A, 12 F, 15B, 22 F, and 33 F, in addition to the PCV13 serotypes. In phase III trials, GMT of serotype 3 was noninferior to PCV13 [19].

Future studies on HSCT recipients are needed to clarify the efficacy of the upcoming PCV15 and PCV20 vaccines. The clinical trial for PCV15 (NCT03565900) in HSCT recipients is currently underway. PCV15 may prevent serotype 3 infections; however, due to the characteristics of serotype 3, caution should be exercised about the possibility of breakthrough infections in HSCT recipients.

Conclusion

Here, we report a case of IPD with serotype 3 pneumonia and empyema in an HSCT recipient who had received three doses of PCV13 and one dose of PPSV23 and had no relapse of AML, GVHD, or use of immunosuppressive agents after HSCT. Whether the breakthrough infection was due to a weak response to the pneumococcal vaccinations or the characteristics of serotype 3 remains unclear. Serotype 3 is known to cause severe complications, warranting caution. Nonetheless, PCV15 may help to prevent infections caused by serotype 3.

Ethics approval and consent to participate

Not applicable.

Authors' contributions

The manuscript has been reviewed and approved by all the authors and is not under consideration for publication elsewhere. All the authors contributed to this work. KI collected clinical data and wrote the initial draft of the manuscript. NM supervised and edited the manuscript. All authors (s) read and approved the final manuscript.

Funding

This study received no funding.

CRediT authorship contribution statement

Kazuhiro Ishikawa: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Nobuyoshi Mori:** Supervision, Writing – review & editing.

Declaration of Competing Interest

All authors have declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

Not applicable.

Author's statement

Kazuhiro Ishikawa wrote the manuscript. Nobuyoshi Mori supervised writing the manuscript.

Consent for publication

Written informed consent was obtained from all patients in this case report. A copy of the written consent form is available to the journal.

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