Specific antibody deficiency to pneumococcal polysaccharide in a young adult with recurrent respiratory infections: a case report

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Abstract

Specific antibody deficiency against pneumococcal serotypes was detected in a patient with recurrent episodes of fever. A 21-year-old man presented with a two-month history of recurrent episodes of fever and shaking chills. He was diagnosed with recurrent episodes of pneumonia caused by *Streptococcus pneumoniae* serotype 19A and treated with amoxicillin. Serotype-specific antibodies were not produced against most of the serotypes, which were consistent with moderate specific antibody deficiency. After pneumococcal 13-valent conjugate vaccination and pneumococcal polysaccharide vaccination, he adequately responded to the infecting serotype with an antibody titer of 1.1 µg/mL. There were eventually no recurrent episodes of fever with pneumonia.

Introduction

Streptococcus pneumoniae is a major pathogen of community-acquired pneumonia, a leading worldwide cause of morbidity and mortality [1]. Various chronic conditions and immune deficiencies predispose individuals to pneumococcal disease, including partial or complete antibody deficiency, complement defects, and congenital or acquired asplenia [2]. The capsular polysaccharides of *Streptococcus pneumoniae* reduce entrapment in the mucus and inhibit complement activity and phagocytosis [3,4]. Antibodies against the external polysaccharide capsule of the pneumococcus, therefore, play a key role in protecting the host against pneumococcal infection by opsonization, which facilitates pneumococcal phagocytosis by leukocytes [5,6].

We report a case of specific antibody deficiency (SAD) against pneumococcal serotypes in a patient with episodes of recurrent fever including pneumococcal pneumonia which were successfully controlled by pneumococcal vaccine to facilitate the early diagnosis of SAD. Both infecting serotype and defective antibody were identified, and the antibody response to pneumococcal polysaccharide vaccination after recovery was analyzed.

Case Report

A 21-year-old Japanese man presented to a local hospital with episodes of fever and shaking chills. These symptoms recurred approximately every two weeks over a two-month period and were present for a few days each time. He did not report headache, cough, or sputum. In early childhood, he had been diagnosed with bronchial asthma, allergic rhinitis and sinusitis, and he uses a fluticasone propionate inhaler. There was no history of smoking,

alcohol intake, or pneumococcal vaccinations, and the patient had no contact with sick people or children.

On examination, his weight was 66 kg, height was 182 cm and body mass index was 19.9 kg/m^2. Body temperature was 36.9°C, heart rate 81 beats/min, blood pressure 137/67 mmHg, respiratory rate 12 breaths/min and oxygen saturation 98% while breathing ambient air. There was no knocking pain on the surface of the face. Cardiovascular examination was normal, lungs were clear to auscultation, and abdominal examination was unremarkable with no hepatosplenomegaly. No peripheral edema or rash were observed, and neurological examination was also unremarkable.

First-visit laboratory findings were normal white blood cell count at 8600 cells/mm^3 (reference range: 3900-9800 cells/mm^3) and there was elevation of the C-reactive protein level at 1.3 mg/dL (reference range: <0.30 mg/dL). Urinalysis was negative for bacteriuria. Chest radiography revealed no opacity in the lung fields (Figure 1A) and blood cultures showed no growth. Fever subsided within a couple of days. Six months later, he visited the hospital again with recurrent episodes of fever, which alleviated spontaneously. Underlying deep abscess was a concern, so nonenhanced computed tomography of the chest and abdomen was performed, revealing nodular shadows in bilateral lower lobes with normal-sized spleen (Figure 2A). One month after that, he visited the hospital again with high fever, headache and rhinorrhea for one day. Chest radiography showed areas of opacity just behind the right hemidiaphragm (Figure 1B), which were identified by chest computed tomography as consolidations in the lower lobe of the right lung (Figure 2B). The white blood cell count was 17,280 cells/mm^3 and the C-reactive protein level was 1.8 mg/dL. *Streptococcus pneumoniae* was detected as the causative microorganism by sputum culture and identified later as serotype 19A measured on a combination of latex immunoassay (Pneumotest-Latex kit; SSI Diagnostica, Hillerød, Denmark) [7] and Quellung reaction method (Pneumococcus Cell Wall Polysaccharide, SSI Diagnostica) [8]. The patient was therefore diagnosed with pneumonia according to the definition of respiratory symptoms and new infiltration that could be recognized on chest radiography or chest computed tomography [9]. The susceptibility of the strains to penicillin G was excellent (minimal inhibitory concentrations, 0.5). Blood cultures showed no growth. He was treated with amoxicillin. Results of immunoglobulins, compliments, IgG subclass assay, serum antibody for human immunodeficiency virus and hemoglobin electrophoresis were normal. Antibody titers against the capsular polysaccharides of 14 pneumococcal serotypes were measured by a multi-analyte immunodetection method (Luminex Corporation, Austin, TX, USA), as previously described (serotypes 1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F, and 23F; Danish nomenclature) [10]. Samples were taken 14 days after diagnosis of pneumonia. The antibody titers were below 0.3 µg/mL against all but pneumococcal serotype 3, 5, 8, and 19F (Table 1), which suggests defective immunity against noninvasive pneumococcal infection including pneumonia [2,11]. Adult patients who have not developed protective antibodies in response to natural infection should be immunized with 13vPCV followed by 23vPPV to protect against various serotypes and to benefit from the priming effect of the conjugate vaccine. Our patient received 0.5 mL of pneumococcal 13-valent conjugate vaccine (13vPCV) 49 days after diagnosis of pneumonia. There was recurrence of pneumonia with a three-day course of fever, headache, sore throat and productive cough 77 days after the initial diagnosis. The white blood cell count was 6 010 cells/mm^3 and the C-reactive protein level was 5.2 mg/dL. *Streptococcus pneumoniae* was detected by sputum culture and later identified to be serotype 19A again. The patient was again treated with amoxicillin with an excellent susceptibility of the strains to penicillin G (minimal inhibitory concentrations, 0.5). There was no subsequent recurrence of pneumonia three months after the initial diagnosis and he received 0.5 mL of 23-valent pneumococcal polysaccharide vaccine (23vPPV) six months after

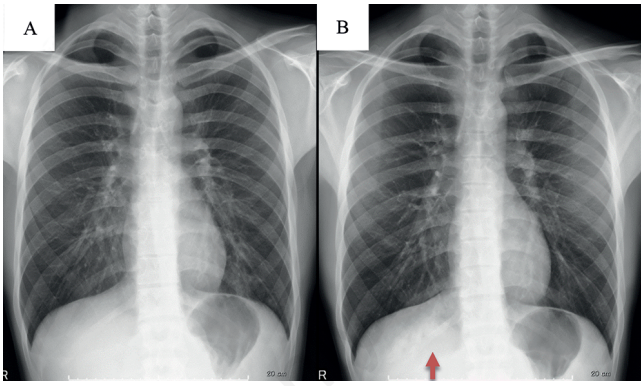

Figure 1. Chest radiography on presentation shows no opacities in the lung fields (A), but in the image taken seven months after the initial visit, there are newly developed opacities just behind the right hemidiaphragm (red arrow) (B).

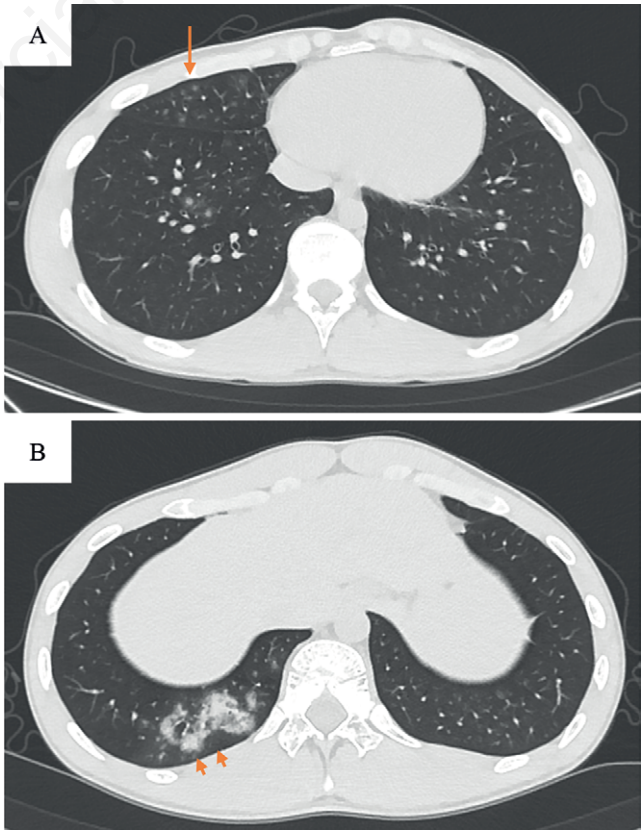

Figure 2. Nonenhanced computed tomography of the chest at six months after the initial visit shows nodular shadows in bilateral lower lobes (red arrow) (A), and in the image taken seven months after the initial visit, consolidations are shown in the lower lobe of the right lung (red arrow heads) (B).

the initial diagnosis of pneumonia. The patient's clinical course is summarized in Figure 3. Fifteen months after the initial diagnosis of pneumonia, antibody titers against the capsular polysaccharides of 23 pneumococcal serotypes were measured by multi-analyte immunodetection method (Luminex) (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F; Danish nomenclature). The antibody titers were below 0.3 µg/mL against pneumococcal serotypes 9V, 10A, 12F, and 23F, even though all of the strains were included in 23vPPV and 9V and 23F in 13vPCV (Table 1). Adequate response (concentration ≥1.3 µg/mL) was seen in less than 70% of the tested serotypes, which is a diagnostic finding of moderate SAD based on the 2015 AAAAI/ACAAI criteria [12]. The antibody titer against pneumococcal serotype 19A was 1.1 µg/mL. There have been no further recurrences of infections since then. The details of this case are reported with the patient's informed consent.

Discussion

Immunological investigation in this case of recurrent fever episodes in a previously stable 21-year-old male revealed an absent pneumococcal antibody response to the infecting serotype, which caused recurrent pneumonia. After vaccination with 13vPCV and 23vPPV following recovery from pneumonia, he no longer had febrile episodes. SAD is characterized by recurrent respiratory tract infections, normal concentrations of IgG, IgA, IgM, and IgG subclasses, and abnormal IgG antibody responses to polysaccharide vaccines. Concentration ≥1.3 µg/mL for <70% of serotypes is proposed as the criteria for moderate SAD for patients aged >6 years according to the 2015 AAAAI/ACAAI criteria [12]. In patients who have previously received PCV, the evaluation might be based solely on the PPV23-exclusive serotypes [13]. Our patient had an impaired response to pneumococcal capsular polysaccharides because he had an adequate response to <70% of the tested serotypes (10 of 23 in all tested serotypes and 4 of 11 in the PPV23-exclusive serotypes), which is consistent with moderate SAD. Antibody responses to conjugate vaccines are normal in patients with specific polysaccharide antibody deficiency [14]. However, not all patients with SAD have a strong serologic response to pneumococcal conjugate vaccine (PCV) [15]. Our patient had an inadequate response to 50% of the tested serotypes (6 of 12), even after vaccination with a conjugate vaccine. Interestingly, although he had an inadequate level of 19A antibodies (1.1 µg/mL), the responsive serotype for the previous recurrent pneumonia, there have been no subsequent recurrent episodes of pneumonia after vaccination with 13vPCV and 23vPPV. The optimal cut-off level for protection from invasive disease is ≥0.3-0.50 µg/mL for healthy children receiving PCV [2,11,16]. Serum antibody correlate of protection threshold levels vary among serotypes, and higher titers may be necessary to

Table 1. Pneumococcal antibodies (µg/mL) during pneumonia and after pneumococcal vaccinations. In bold the serotype detected in our patient.

Pneumococcal serotype	14 days after the initial diagnosis of pneumonia	Post-vaccination with 13vPCV and 23vPPV (15 months after the initial diagnosis of pneumonia)
Serotypes covered by 13vPCV and 23vPPV		
1	≤0.3	0.7
3	0.5	1.3
4	≤0.3	1.0
5	1.0	7.2
6B	≤0.3	0.4
7F	≤0.3	1.5
9V	≤0.3	≤0.3
14	0.3	2.8
18C	≤0.3	2.1
19A	N/A	1.1
19F	1.9	14.6
23F	≤0.3	≤0.3
Serotypes covered only by 23vPPV		
2	N/A	20.3
8	0.9	10.2
9N	≤0.3	1.1
10A	N/A	≤0.3
11A	N/A	2.0
12F	≤0.3	≤0.3
15B	N/A	6.0
17F	N/A	0.9
20	N/A	1.2
22F	N/A	1.1
33F	N/A	0.7

13vPCV, 13-valent conjugate vaccine; 23vPPV, 23-valent pneumococcal polysaccharide vaccine; N/A, not available.

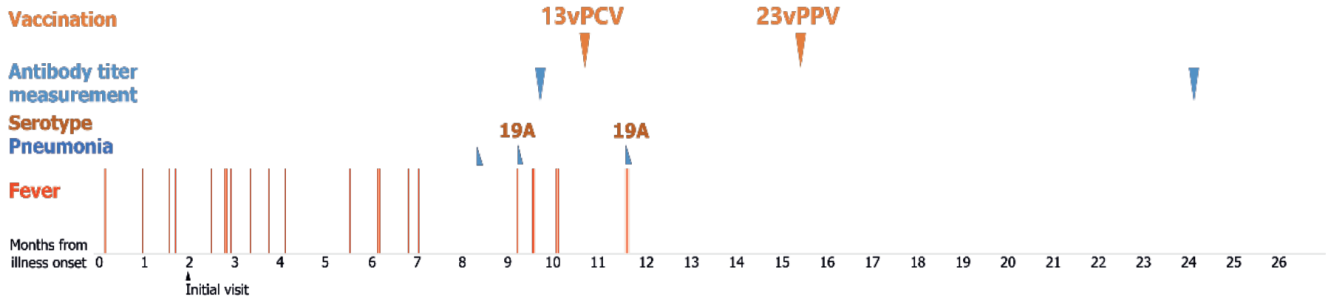

Figure 3. Clinical course of the patient. Fever is defined as a temperature over 37.5°C. 13vPCV, 13-valent conjugate vaccine; 23vPPV, 23-valent pneumococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; SAD, specific antibody deficiency.

protect from noninvasive infections such as pneumonia, otitis media, and sinusitis [17]. The correlate of protection value for invasive pneumococcal disease for serotype 19A is reported as 1 µg/mL [18], which might explain why our patient was free from invasive pneumococcal disease.

Our patient had recurrent pneumonia one month after vaccination with 13vPCV, which was considered to be a breakthrough infection with serotype 19A. Serotype 19A is one of the main serotypes associated with breakthrough infection [19], which may be explained by several factors. First, pneumococcal carriership at the time of vaccination is associated with a lower response to that serotype [20]. Next, during pneumococcal infection, a high load of circulating polysaccharide antigens can cause temporary immune paralysis [21]. Furthermore, certain genomic strain is associated with vaccine failures/breakthrough cases [22]. Our patient remained free from febrile episodes, so he might have acquired a sufficient antibody level to serotype 19A.

Immunization with 13vPCV is a first step in the management of SAD. Measurement of antibodies 4 to 6 weeks after the last immunization and monitoring for infections are recommended [23]. If there is no serological and clinical response, further investigation into the immunity is required. Regarding the therapeutic approach to SAD in our patient, antibodies were measured 14 months after 13vPCV because he lived far from our hospital and the titer was checked when he returned to his hometown. Although adequate response was seen in less than 70% of the tested serotypes including 19A, he remained clinically stable, so refrained from further immunization. If a patient has failed to respond to a 13vPCV dose but maintains an abnormal pattern of infection, reimmunization with 23vPPV after one year may produce a better response in terms of the priming effect of the conjugate vaccine [13].

In conclusion, SAD against pneumococcal serotypes is a primary antibody deficiency that should be immediately considered in adults who develop recurrent fever with pneumonia. Patient education and the administration of conjugate vaccines may contribute to prophylaxis of pneumonia episodes in these patients.

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