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CASE REPORT

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A pediatric case series of invasive pneumococcal disease caused by *S.Pneumonia* serotype-19A despite full dose vaccination

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ABSTRACT

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia and bacterial meningitis in children. Although pneumococcal conjugate vaccines (PCVs) are commonly available, invasive pneumococcal disease (IPD) still remains a life-threatening complication. Serotype 19A has high invasive potential and is capable of causing extensive and destructive lung disease. This strain has greater invasive potential, may have a growth advantage over other pneumococcal serotypes in normally sterile sites, and is often resistant to multiple antibiotics. Although being a component of PCV13 vaccine, serotype 19A may still be seen in fully vaccinated children and can cause invasive disease. Herein, we present four cases of IPD caused by *S. pneumoniae* serotype 19A who received the full regimen of PCV13 vaccination.

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Pneumococci serotype 19; invasive pneumococcal disease; pediatric

Introduction

Streptococcus pneumoniae is the leading cause of community-acquired pneumonia in children.[1,2] Although pneumococcal conjugate vaccines (PCVs) are commonly available, invasive pneumococcal disease still (IPD) remains a life-threatening complication. In the past decade, the incidence of pneumococcal pneumonia complications such as necrotizing pneumonia (NP) and/or empyema has increased among children.[2,3] Especially when complicated by bronchopleural fistula, NP is associated with greater morbidity, longer duration of pleural drainage, and prolonged hospitalization.[4]

S. pneumoniae is also the most common cause of bacterial meningitis in infants and children older than one month of age. The incidence of pneumococcal meningitis declined after the introduction of routine vaccination against pneumococcus. However, despite decades of vaccination, pneumococcal meningitis remains an important cause of childhood morbidity and mortality, with an estimated annual incidence of approximately 0.8 per 100.000 people in the United States.[5] These vaccines again reduced disease caused by vaccine serotypes by > 90%, but overall rates of disease were largely sustained by serotype replacement.[6]

Pneumococcal congugated vaccine PCV 7 was introduced in 2008 in Turkey, pediatric vaccine schedule, whereas PCV 13 was introduced in 2011.[7] The routine schedule for PCV 13 includes a two-dose primary series (2 and 6 months) and a booster dose (12 months).[7] However, vaccine-induced protection from pneumonia remains modest at best, in contrast to potent efficacy against bacteremia. Besides PVC 13 vaccination, between 2014 and 2017, 50 of 119 (42%) isolates from children hospitalized with culture-proven pneumococcal pneumonia at the eight children's hospitals in the United States Pediatric Multicenter Pneumococcal Surveillance Study Group were PCV13 serotypes; 19A and 3 were most common.[8] They are prominent causes of pneumonia and parapneumonic effusion, although being a component of PCV13.[2,9] Verbal consent was obtained from the families.

Herein, we present four cases of IPD caused by *S. pneumoniae* serotype 19A who received the full regimen of PCV13 vaccination (Table 1).

Case reports

Case 1

A 3-year-old previously healthy girl was consulted with intermittent fever and a productive cough for 4 days. She also had shortness of breath and irritability for 1 day before presentation to the pediatric emergency department. She was fully vaccinated with PCV 13 series. On physical examination, she had fever, tachpynea, and tachycardia. She had decreased breath sounds over the left lung field, with diffuse crackles over both lungs. Chest radiograph demonstrated consolidation of the left lung with pleural effusion and also infiltration on right paracardiac zone but no cardiomegaly.

Her laboratory tests revealed leukocytosis (30000/mm^3) with 39% bands, 55% neutrophils, and 3% lymphocytes; C-reactive protein (CRP) was 259 mg/L (0–6). Chest radiograph and computed tomography (CT) demonstrated consolidation in the left middle and lower zones of lung and parts of the right middle and lower lobes, with air bronchogram accompanied by a 4 cm

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Table 1. Clinical features of cases with invasive pneumococcal disease.

Characteristic	Case 1	Case 2	Case 3	Case 4
Age (years)	3	5	3,5	3
Sex	Girl	Boy	Girl	Girl
Sign(s) and symptom(s)	Fever, productive cough, shortness of breath	Fever, cough	fever, unconsciousness, otalgia	Fever, otalgia
Symptom duration before hospitalization (days)	4	5	5	4
Prior antibiotic use before sample collection	Amoxicilline clavulonate	Amoxicilline clavulonate	Amoxicilline clavulonate	None
Clinical presentation	Necrotizing pneumonia+ Empyema	Empyema	Bacterial meningitis + MODS	Acute otitis media + Bacterial meningitis
Vaccine History	PCV 13	PCV 13	PCV 13	PCV 13
Underlying Illness	None	Apert Syndrome	None	None
Antibiotic regimen	Ceftriaxone + Vancomycin	Ampicillin sulbactam	Ceftriaxone + Vancomycin	Ceftriaxone + Vancomycin
Sterile site of S. pneumoniae 19A isolation	Blood and pleural fluid	Blood	Cerebrospinal fluid	Blood
Antibiotic susceptibility	Susceptibile to penicillin	Susceptibile to penicillin	Penicillin and ceftriaxone resistant	Penicillin and ceftriaxone resistant
Length of stay (day)	21	14	65	14
Outcome	Survived	Survived	Survived	Survived

PCV: Pneumococcal conjugate vaccines, MODS: Multiorgan dysfunction syndrome.

left pleural effusion. Intravenous vancomycin (60 mg/kg/day) and ceftriaxone (100 mg/kg/day) were administered. Left-sided closed-tube thoracostomy drainage was undertaken. Pleural fluid analysis was compatible with exuda. Gram-stain of the empyema demonstrated gram-positive diplococci and wright-stain demonstrated 90% polymorphonuclear leukocyte. She received intrapleural urokinase treatment for three days at a dose of 40.000 units in 40 mL 0.9% saline twice daily (with a four-hour dwell time). On day 5, *S. pneumoniae* grew in both blood culture and pleural fluid culture. *S. pneumoniae* was susceptibile to penicillin. The serotype of isolates was subsequently identified as 19A by the capsular swelling method (Quellung reaction) using commercially available antisera from the Statens Serum Institut (Coperhagen, Denmark).

Her acute phase reactants regressed incrementally. She was discharged from hospital on the 21th day, with no complaints with CRP 6 mg/L and leukocyte count 12,000/mm^3.

Case 2

A 5-year-old patient diagnosed with Apert Syndrome, coanal atresia, pyloric stenosis, craniosinositosis, inguinal hernia, hydrocephalus, ventriculo peritoneal shunt, nephrolithiasis, and secundum asd applied with the complaints of fever and cough for the last 5 days.

On physical examination, he had fever, tachypnea, and hypoxia. He had crackles over the upper zone of the right lung. Gram-stain of the empyema demonstrated gram-positive cocci and wright-stain demonstrated 80% polymorphonuclear leukocyte. Ampicillin sulbactam (150 mg/kg/day) was initiated. There was no pleural fluid on thorax ultrasonography. *S.pneumonia* grew in blood culture on follow-up, and the serotype of isolate was subsequently identified as 19A. The isolate was susceptible to penicillin.

Case 3

A three and a half year old girl was consulted with fever and unconsciousness. She had fever and otalgia for the last 5 days. She was initiated amoxicilline clavulonate therapy. On her follow-up, fever resolved but headache, light irritability, and unconsciousness were observed.

On physical examination, she had lethargia, tachycardia, and neck stiffness. Blood work showed leukocytosis (29500/mm^3) with 85% neutrophils and 3% lymphocytes; CRP was 181 mg/L (0–6).

Lumbar puncture was performed. On direct visualization, there were 200 leukocyte/mm^3, cerebrospinal fluid protein was 308 mg/dL, cerebrospinal fluid glucose was 8 mg/dL, compatible with bacterial meningitis. Intravenous vancomycin (60 mg/kg/day) and ceftriaxone (100 mg/kg/day) were administered.

In a few hours, hypotension and purpuric rash were revealed. She was admitted to intensive care unit because of sepsis and disseminated intravascular coagulation. Thrombocytopenia and acute renal failure developed on follow-up. She needed several times of hemodialysis, fresh frozen plasma, and platelet support.

On follow-up, *S. pneumonia* grew on blood and cerebrospinal fluid culture. The serotype of isolates was subsequently identified as 19A. The isolate was penicillin and ceftriaxone resistant and vancomycin susceptible. She was hospitalized for 65 days.

Case 4

A three year old, previously healthy girl, was consulted with fever and otalgia for four days. Her vital signs were normal for age. She was hopitalized for inability to maintain hydration orally, and ceftriaxone therapy was initiated (100 mg/kg/day). Her physical examination was initially normal except for acute otitis media. On her follow-up, unconsciousnesss and neck stiffness occured. Lumbar puncture was performed. On direct visualization, there were 900 leukocyte/mm^3, cerebrospinal fluid protein was 208 mg/dL, cerebrospinal fluid glucose was 28 mg/dL, compatible with bacterial meningitis. Intravenous vancomycin (60 mg/kg/day) was added to therapy. *S. pneumonia* grew on her blood culture which was obtained before ceftriaxone therapy. Cerebrospinal fluid culture was

steril probably due to the fact that the procedure was performed after the treatment. The serotype of isolate was subsequently identified as 19A. The isolate was penicillin and ceftriaxone resistant. She was hospitalized for 14 days and discharged without any complication.

Discussion

The term invasive pneumococcal disease is used for more severe and invasive pneumococcal infections, such as bacteremia, sepsis, meningitis, and osteomyelitis, NP in which the bacterium can be isolated from normally sterile sites.[10] The incidence of CAP declined in many countries after the introduction of PCVs, but rates of complicated pneumonia have increased during the last two decades.[5,9] The incidence of 'all-cause' empyema in children 2–4 years increased from 3.7 cases per 100,000 in 1996–8 to 10.3 cases per 100,000 in 2005–7 in the United States (US).[11] Cases of NP in children are reported worldwide.[7] Necrotising pneumonia is commonly caused by pneumococci and *S. aureus*. [12]

Serotypes 3 and 19A were most closely associated with pneumococcal NP among vaccine strains.[13] In surveillance from eight children's hospitals after licensure of PCV13, IPD due to serotype 19A declined substantially, but remains one of the most frequently isolated serotypes.[8] In Centers for Disease Control and Prevention (CDC) surveillance of IPD in children <5 years of age, serotype 19A remains a common cause of IPD due to PCV13 serotypes.[14] In the USA, PCV13 was found to be 85.6% effective against serotypes 19A.[13] There are few studies on the epidemiology of 19A in Turkey. In a study conducted between 2010 and 2012, 156 pediatric patients who received pneumonia complicated with empyema in 13 hospitals from seven surgical regions of Turkey were included. The serotypes of *S. pneumoniae* were specified in 33 of 156 samples. One patient had serotype 19A.[15] In the multicenter, hospital-based, epidemiological study conducted by Ceyhan et al. between 2015 and 2018, a total of 167 cases were diagnosed with invasive pneumococcal disease. The most common serotypes were 19F (11.9%). However, serotype 19A was seen in 4.1%.[16]

Serotype 19A has high invasive potential and is capable of causing extensive and destructive lung disease. This strain has greater invasive potential, may have a growth advantage over other pneumococcal serotypes in normally sterile sites, and is often resistant to multiple antibiotics.[17] Due to the genetic variation of serotype A, it may have acquired resistance to antibodies and is related to invasive disease despite vaccination.[18]

Resistance of pneumococci against antibiotics varies regionally. At present, in the USA when usual doses of parenteral penicillin are used to treat pneumococcal infection that does not involve the CNS, 96% of isolates are susceptible, 2% are intermediate, and 2% are resistant.[19] Besides, 97.6% of pneumococci are susceptible, 1.9% are intermediate, and 0.3% are resistant to ceftriaxone and cefotaxime.[19] According to the Asian Network for Surveillance of Resistant Pathogens (ANSORP) study, among nonmeningeal isolates, the prevalence rate of penicillin-nonsusceptible pneumococci was 4.6% and penicillin resistance was extremely rare (0.7%). Multidrug resistance was observed in 59.3% of isolates from Asian countries. Major serotypes were 19F (23.5%), 23F (10.0%), 19A (8.2%), 14 (7.3%), and 6B (7.3%). Serotypes 19A (8.2%), 3 (6.2%), and 6A (4.2%) were the most prominent non-PCV7 serotypes in the Asian region. Among isolates with serotype 19A, 86.0% and 79.8% showed erythromycin resistance and MDR, respectively.[20] A report of the The SENTRY Antimicrobial Surveillance Program stated that penicillin susceptibility rates were decreased from 67.6% in 1997–1998 to 41.6% 2007–2008 in Asia Pacific region. MDR rates were highest in the Asia Pacific region compared to other geographic regions, with an overall rate of 41.2% (varying from 23.7% in 1997–1998 to 53.3% in 2007–2008).[21] Penicillin susceptibility was 84.4% and ceftriaxone susceptibility was 83.2% according to an adult surveillance study in our country.[22]

The antimicrobial susceptibility of isolates in our patients were, penicillin susceptible in case 1 and 2, penicillin resistant & ceftriaxone intermediate resistant in case 3 and 4.

In conclusion, despite the introduction of broad serotype coverage with PCV13 and widespread use of antibiotics, severe IPD remains a possible life-threatening disorder. This case series highlights IPD in healthy and fully vaccinated pediatric patients. Besides, serotpye 19A is still challanging as the cause of IPD although it is included in PCV13. Further research is required for boosters and genetic variation of serotype 19A.

In case of IPD, empirical treatment active against the main bacterial species (*S. pneumoniae*) should be started immediately, and as in our case series, penicillin and also ceftriaxone resistance should be kept in mind while intiating antimicrobial therapy.

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