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Case Report

Pediatric case of septic arthritis due to *Streptococcus pneumoniae* serotype 19A

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ABSTRACT

In recent years, the incidence of pediatric septic arthritis caused by *Streptococcus pneumoniae* has been quite low. The pneumococcal conjugate vaccine PCV10 is the available vaccine included in the Bulgarian national immunization program. PCV10 reduces the incidence of invasive diseases, but non-vaccinal serotypes like 19A, the etiologic agent of the case of septic arthritis reported herein in a 3-year-old boy. The synovial fluid was positive for *S. pneumoniae*. The patient was treated with vancomycin during hospitalization and trimethoprim/sulfamethoxazole was recommended for at-home treatment. The isolate was subjected to latex agglutination, antimicrobial susceptibility testing, PCR detection for macrolide-resistance genes, and MLST. The strain revealed ST695 and a genotype previously associated with vaccine serotype 4. The incidence of pneumococcal infections caused by capsule-switching events and non-PCV10 serotypes is expected to increase.

Introduction

Septic arthritis (SA) is a severe inflammation that affects the joint fluid and tissues and requires prompt diagnosis and treatment. The most common causative agent of this infection in children is *Staphylococcus aureus*.[1-3] Bacterial SA is also caused by *Streptococcus pyogenes, Kingella kingae*, and rarely with *Streptococcus pneumoniae*.[1,2,4] According to an European study from 2021,[1] just 6.5% of pediatric osteoarticular infections are caused by *S. pneumoniae*. Cohen et al.[2] reported pneumococcal SA in 1.6% of the investigated children. Osei et al. found no case of *S. pneumoniae* in patients with SA.[5]

S. pneumoniae is a vaccine-preventable agent. Since April 2010, PCV10 (Synflorix) is licensed for routine immunization in Bulgaria. The vaccination schedule for PCV10 in our country is carried out with two vaccines at two and four months of age and re-immunization with one vaccine at 12 months of age. The PCV10 reduce dramatically the incidence of invasive pneumococcal disease but also result in the spread of new emergent and adaptive non-vaccine serotypes. Pneumococcal serotypes associated with invasive infections in children vary between different countries. In Canada, the serotypes 7F, 19A, and 33F were predominant,[6] whereas in China 19F was most common, followed by 19A, 14, 23F, 6A, and 6B.[7]

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Detection of *S. pneumoniae* in normally sterile sites of the human body is of great importance for clinical and epidemiological purposes.

Case presentation

A 3-year-old boy had initial symptoms of fever (38.6 °C), vomiting, limping, and swelling of the right knee. Two days later, in middle of June 2021, the child was hospitalized at the Department of Pediatric Diseases of Dr. Georgi Stranski University Hospital, Pleven, Bulgaria, with subfebrile temperature (37.6 °C), weakness, fatigue, tachypnea, redness and increased swelling of the right knee, very painful passive movements in the affected joint, and inability to walk. The laboratory tests showed significant leukocytosis – 28.3 × 10^9/L with 88.7% neutrophils, and a high level of C-reactive protein (CRP) – 177.19 mg/l (Table 1). Computed tomography of the knee revealed a collection of synovial fluid in the joint space of the right knee and soft tissue edema around the patella. Joint aspiration was done and the Gram stain revealed presence of Gram-positive diplococci, and >10 polymorphonuclear cells per high-power field. In addition, 63.2 × 10^9/L white blood cells count with 79% neutrophils was detected in the synovial aspirate. The patient was initially treated with a combination of meropenem and amikacin. After isolation of the infection agent, vancomycin was used in the hospital and trimethoprim/sulfamethoxazole was recommended for at-home treatment.

According to the immunization schedule of Bulgaria, the boy had been regularly vaccinated. There was no history of previous diseases and specifically no infection of the airways. During the current hospitalization, no comorbidities were diagnosed in the patient. The tested nasopharyngeal swab was negative.

The synovial fluid was positive for *S. pneumoniae*, identified by Vitek2 Compact system (*bioMérieux, France*). In addition, PCR for the major pneumococcal autolysin confirmed the causative agent of the SA. The lytA-based PCR is used to distinguish *S. pneumoniae* from other streptococci.[8] Serotyping of *S. pneumoniae* was performed using the latex agglutination factor antisera provided by Statens Serum Institut (*Pneumotest-Latex kit; SSI*) and the serotype 19A was determined.

Table 1 – Initial laboratory blood tests of a 3-year boy with septic arthritis.

Parameters	Results	Normal reference range
White blood cell count	28.3	3.5 – 10.5 × 10^9/l
Neutrophils	88.7	40 – 76%
Lymphocytes	8.5	20 – 48%
Monocytes	2.5%	1 – 11%
Erythrocytes	3.02	4.4 – 5.9 × 10^{12}/l
Hemoglobin	90.0	135 – 180 g/l
Hematocrit	0.238	0.40 – 0.53 l/l
Thrombocytes	292.0	130 – 360 × 10^9/l
Erythrocyte sedimentation rate	31	0 – 18 mm/h
Fibrinogen	5.9	2 – 4 g/l
C-reactive protein	177.19	0 – 5 mg/l
Alanine aminotransferase	11.4	0 – 40 U/l
Albumin	33.8	35 – 52 g/l
Alkaline phosphatase	148.0	40 – 129 U/l
Aspartate aminotransferase	25.2	0 – 40 U/l
Gamma-glutamyl transferase	15.0	0 – 60 U/l
Creatinine	22.0	53 – 115 μmol/L
Total protein	61.2	66 – 87 g/l
Glucose	4.88	4.1 – 6.1 mm/l

Routine antimicrobial susceptibility testing was carried out using Vitek2 Compact system. Additionally, a broth microdilution method was performed using the Sensitre custom plate format (TREK diagnostic systems), Plate code: STP6F, and according to the European Committee on Antimicrobial Susceptibility Testing breakpoints and criteria for non-meningitis isolates.[9] The tested antimicrobials were: Moxifloxacin, Levofloxacin, Tetracycline, Cefuroxime, Ceftriaxone, Cefotaxime, Daptomycin, Chloramphenicol, Penicillin, Meropenem, Ertapenem, Amoxicillin/Clavulanic acid 2:1 ratio, Linezolid, Clindamycin, Cefepime, Tigecycline, Azithromycin, Erythromycin, Trimethoprim/ Sulfamethoxazole, Vancomycin. *S. pneumoniae* ATCC 49,619 was used as a control strain in susceptibility testing. The presence of macrolide resistance was determined by PCR reactions for the expression of *ermB* and *mefE* genes with primers sets designed by Sutcliffe et al.[10] The strain showed dual macrolide resistance, in presence of both *ermB* and *mefE* genes with high MIC values (MIC > 256 mg/l) and susceptibility to all other tested antibiotics.

MLST was carried out as described by Enright.[11] Briefly, seven housekeeping genes were sequenced and compared to the pneumococcal MLST database (http://pubmlst.org/spneumoniae) to identify the allelic profile and the sequence type (ST). GPSC type of ST was determined using the Global Pneumococcal Sequencing Project: https://www.pneumogen.net. Genetic relatedness to reference pneumococcal clones was confirmed in the Pneumococcal Molecular Epidemiology Network (PMEN). The MLST analysis disclosed ST695, which is categorized as GPSC type 27.

Discussion

To our knowledge, this is the first described medical case of pediatric SA caused by 19A *S. pneumoniae* in Bulgaria.

The pneumococcal vaccine implemented by the Bulgarian immunization program is PCV10. In our country, no other pneumococcal vaccines were used before PCV10 introduction, nor PCV7 for infants, neither the 23-pneumococcal polysaccharide vaccine (PPSV23) for adults. According to the national epidemiological data, 90.3% of newborn children in Bulgaria were vaccinated with PCV10 in 2014–2020 (National Center of Health Information). PCV13 can be purchased in the pharmacy market, and PCV15 is still not licensed in our country.

Following the PCV10 introduction, there has been a significant decline both in invasive pneumococcal diseases and non-bacteremic pneumonia. The most prevalent serotypes in the last years in our geographic area are 19A (13.8%), 6C (11.7%), 3 (9.6%), 15A (8.3%), and 23A (5.5%), which are non-PCV10 serotypes.[12]

The pneumococcal serotype in the described case was 19A, which has high virulence and global distribution. It usually causes mucosal and invasive diseases, but is a very rare causative agent in SA in children.

Before PCV10 implementation in 2009, 19A was already a common serotype recovered from middle-ear infection and from invasive and non-invasive pneumococcal infections in Bulgaria. In the post-vaccine era, the non-PCV10 serotype 19A emerged and occupied a leading position in the serotype distribution among vaccinated children.[12] The serotype 19A has successfully spread in our geographic area and a large number of 19A isolates developed multidrug resistance.[12] Our study disclosed a dual macrolide resistance for the tested strain. Factors, such as high antibiotic consumption, vaccine pressure by the usage of PCVs, clonal expansion of existing clones, and the emergence of new clones, have been implicated in the wide distribution of serotype 19A isolates.[13]

The 19A isolates took part in different CCs, but the most predominant in our country were MDR CC320, sharing five identical alleles with PMEN clone Taiwan19F-14, and CC230, representing the international Denmark14-ST230 clone.

CC320 was the most disseminated clone in Bulgaria during the last 10 years.[5] The emergence of ST320 among 19A isolates increased also in the USA and other European countries in the postvaccine era.[7]

The genotypic characterization of the analyzed *S. pneumoniae* isolate showed ST695, which is clustered in international GPSC type 27. The strain has a genotype previously associated in the global pneumococcal sequencing collection with vaccine serotype 4 but expressed a non-PCV10 serotype 19A capsule. The global pneumococcal dataset listed that GPSC type 27 is also found in the USA, Israel, and Palestina.

ST695 belonged to GPSC type 27, which comprised also ST205, and represented the international PMEN clone Sweden4–38. It may suggest a capsule switch due to a recombination event between the donor ST205 of the vaccine serotype 4 and the recipient ST695 of non-PCV10 serotype 19A.

This vaccine-escape recombinant strain can be assumed as a result of the expansion of preexisting serotype 4 clones circulating before PCV10-vaccine implementation in our country.

Conclusion

Prompt diagnosis and adequate treatment of infectious arthritis can help prevent significant morbidity and mortality. Our case underscored the need for continuous monitoring of the serotype changes. The incidence of pneumococcal infections caused by non-PCV10 serotypes is expected to increase in the future.

Conflicts of interest

The authors declare no conflicts of interest.

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