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Case Report/
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A Multiple Drug-Resistant *Streptococcus pneumoniae* Caused Acute Otitis Media

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ABSTRACT

Acute otitis media (AOM), known to be a common pediatric disease is a suppurative infection of the middle ear and air spaces. Causative agent of AOM is often *Streptococcus pneumoniae* in all the world's children. In the last decades there has been a striking increase in the incidence of penicillin-resistant and multiply antibiotic-resistant pneumococci. The high prevalence of multi-drug resistant *S. pneumoniae* is a clinical problem for medical personnel in the selection of empiric antibacterial treatments. Here we notify a case of a 9-month-old boy with bilateral acute otitis media caused by multi-drug resistant *S. pneumoniae*. A multiple drug-resistant *S. pneumoniae* strain was isolated in otorrhea sample obtained from bilateral middle ear of the child with complaints of persistent otitis media. Antibiotic sensibilities were analyzed with disc diffusion and E-test method. The detection of pneumococcal serotype was determined by capsular swelling reaction and sequence type was conducted by multilocus sequence typing (MLST). The serotype was determined as 19A and the sequence type was found ST199. These case report were evaluated in order to draw attention to the increase of pneumococcal AOM infections with multi-drug resistant in among children.

Key words: Acute otitis media, Children, Multiple drug-resistant, *Streptococcus pneumoniae*.

Çoklu İlaç Dirençli *Streptococcus pneumoniae* Kaynaklı Akut Otitis Media

ÖZET

Akut otitis media (AOM) orta kulak ve hava boşluklarının süpüratif enfeksiyonu olup, yaygın bir pediatrik hastalıktır. AOM'nin etkensel ajanı, tüm dünya çocuklarında sıklıkla *Streptococcus pneumoniae*'dir. Son birkaç on yılda, penisiline dirençli ve çoklu ilaca dirençli pnömokok insidansında çarpıcı bir artış olmuştur. Çoklu ilaca dirençli *S. pneumoniae*'nin yüksek prevalansı, ampirik antimikrobiyal tedavi seçiminde uygulayıcılar için klinik bir zorluktur. Bu yazıda, çoklu ilaca dirençli *S. pneumoniae*'nin neden olduğu iki taraflı akut otitis media'sı olan 9 aylık bir erkek olgu sunuldu. Persistan otitis media şikayeti olan çocuğun iki taraflı orta kulağından elde edilen akıntı örneğinde çoklu ilaca dirençli bir *S. pneumoniae* suşu izole edildi. Antibiyotik duyarlılıkları disk difüzyon ve E-test yöntemiyle analiz edildi. Pnömokokal serotip tespiti kapsüler şişme reaksiyonu ile belirlendi ve sekans tipi multilokus dizilimiyle (MLST) yapıldı. Serotip 19A olarak belirlendi ve dizi tipi ST199 olarak bulundu. Çocuklarda çoklu ilaca dirençli pnömokokal AOM infeksiyonlarının artışına dikkat çekmek amacıyla bu olgu sunumu değerlendirilmiştir.

Anahtar kelimeler: Çocuklar, Çoklu ilaç direnci, MLST, *Streptococcus pneumoniae*.

INTRODUCTION

Acute otitis media (AOM) is a widespread pediatric disease. Ninety percent of children experience at least one ear infection before starting school and particularly, it is relatively common among children between six months to three years of age. The most frequent bacterial pathogen in AOM is *Streptococcus pneumoniae*, followed by *Haemophilus influenzae* and *Moraxella catarrhalis* (Le Saux et al. 2016; Orlando et al. 2019).

Bacterial resistance to antimicrobial agents is a rapidly increasing problem worldwide. The similar reports were published from all over the world after the first isolation of penicillin-resistant pneumococci in the mid-1960s (Aşkar ve Deveboynu 2018; Xu et al. 2009) . Penicillin-resistant *S. pneumoniae* strains can also be resistant to other classes of antibiotics like cephalosporins, macrolides, sulfonamides, trimethoprim-sulfamethoxazole, quinolones, chloramphenicol and tetracyclines (Kilian 2012). Resistance is usually obtained as part of a gene cassette or a transposon, which encodes resistance to multiple antibiotics (Fair and Tor 2014). The emergence of such antimicrobial resistance may cause to failure in the treatment of pneumococcal infection (EUCAST 2019). This case report was presented in order to draw attention to the necessity of the early diagnosis and emergency treatment of AOM infections caused by multidrug-resistant *S. pneumoniae* isolates in among children, and to the importance of the vaccination, implementation of conservation and control measures.

Case Presentation

A 9-month-old boy presents with the chief complaints of the ear pain of 22 hours' duration, a slight cough, irritability and fever. He had received many times different antibiotics, because of his recurrent ear pain, before he was admitted to an outpatient clinic in Istanbul. On his physical examination, it was found erythema, bullying and middle ear effusion. His rectal temperature was recorded at 39° C. The anemia was determined in his peripheral hemogram examination. His illness was diagnosed as bilateral acute otitis media. The swab specimens from his both ears were obtained for culture and cefuroxime axetil 30 mg/kg/day, orally in two divided doses were given. The both ears were found to be filled with pus when he returned to the clinic for control three days later.

S. pneumoniae was isolated as a single organism in cultures from both ears of the patient, by colonial morphology, Gram staining, bile solubility, and optochin susceptibility. Antimicrobial susceptibilities of the *S. pneumoniae* were detected using the disk diffusion and E-test method. The findings were evaluated according to the European Committee on Antimicrobial Susceptibility Testing criteria (EUCAST 2019).

S. pneumoniae strain was resistant to penicillin, erythromycin, trimethoprim-sulfamethoxazole, tetracycline and clindamycin by the disk diffusion. The isolate was transferred to Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Department of Medical Microbiology Laboratory for confirmed by conventional antimicrobial susceptibility testing, as soon as the multiple drug-resistant to *S. pneumoniae* was determined. The child was transferred to the Acıbadem University hospital for intravenous treatment and aspiration. Intravenous ceftriaxone (100mg/kg/day) and vancomycin (15 mg/kg/every 12h) were started for a period of 4 days, with by aspiration, due to the failure of previous cefuroxime treatment. The child responded well to treatment and a great clinical improvement was recorded.

The causative bacteria was confirmed as a strain of penicillin-resistant *S. pneumoniae* using the VITEK® automated identification and susceptibility testing system (bioMérieux, Marcy l'Etoile, France). Also, the susceptibility of *S. pneumoniae* was quantified by measuring the minimum inhibitory concentrations (MICs) for antibiotics using the E-test (AB Biodisk, Solna, Sweden) based on guidelines from EUCAST standards. Quality-control organisms including *S. pneumoniae* ATCC 49619 and Escherichia coli ATCC 35218 were used. *S. pneumoniae* strain was resistant to penicillin, amoxicillin-clavulanic acid, erythromycin, trimethoprim-sulfamethoxazole, tetracycline and clindamycin. They were confirmed for the minimum inhibitory concentration (MIC) by E test method. *S. pneumoniae* strain was found resistant to penicillin, amoxicillin-clavulanic acid, erythromycin, trimethoprim-sulfamethoxazole, tetracycline and clindamycin. It was susceptible to cefepime, ceftriaxone, cefotaxime vancomycin, levofloxacin and rifampin (Table 1).

Table 1: Antibiotic Susceptibility Test Results of *S. pneumoniae*

Antimicrobial Agent	Disk content	Zone diameter breakpoints	MIC breakpoints	S ≤	R >
Penicillin*	1µg oxacillin	R	R	0.06	2
Amoxicillin-clavulanic acid	-	-	R	0.5	1
Cefepime	-	-	S	1	2
Cefotaxime	-	-	S	0.5	2
Ceftriaxone	-	-	S	0.5	2
Vancomycin	5 µg	S	-	2	2
Erythromycin	15 µg	R	R	0.25	0.5
Tetracycline	30 µg	R	R	1	2
Levofloxacin	5 µg	S	-	2	2
Trimethoprim-sulfamethoxazole	1.25-23.75 µg	R	R	1	2
Rifampisin	5 µg	S	-	0.06	0.5
Clindamycin	2 µg	R	R	0.5	0.5

S: Susceptible, R: Resistant

* Nonmeningitis

Serotyping was conducted by capsular swelling reaction using commercial serogroup and serotype specific antisera (Statenserum Institute) according to the manufacturer's instructions. The serotype was determined as 19A. The sequence type was performed by multilocus sequence typing (MLST) as previously described (Enright and Spratt 1998) and the sequence type was found ST199 by comparing the sequences with alleles downloaded from the pneumococcal MLST database (http://spneumoniae.mlst.net). Clonal complexes were appointed using the eBURST algorithm using the software available at the MLST website (http://www.mlst.net). The child is doing well at the time of this writing.

DISCUSSION

Otitis media, which is among the most common childhood disease, is responsible for approximately one-third of those who visit the health centers (Nuorti et al. 2010; Vergison et al. 2010). This disease is usually suppurative and *S. pneumoniae* is the predominant organism. The prevalence of *S. pneumoniae* carriage in healthy children, <5 years of age ranged from 20% to 93.4% in low income countries and from 6.5% to 69.8% in lower-middle income countries (Adegbola et al. 2014). Rate of *S. pneumoniae* carriage alterable according to age, geographic region and the population (Peter and Klein 2008). Enginyurt et al. reported that the nasopharyngeal carriage rate was between 2.8% and 43% in healthy Turkish children (Enginyurt et al. 2016). Generally, carriage is acquired within the early months of life and sustained in older children and adults at lower levels (Adegbola et al. 2014).

For many years, pneumococci were susceptible to penicillin. In several countries, 50-80% of strains are no longer susceptible to penicillin (Kilian 2012). Penicillin resistance in *S. pneumoniae* is because of the alteration of penicillin-binding proteins and it is often associated with resistance to multiple classes antibiotics. In penicillin-resistant *S. pneumoniae* strains, resistance to macrolides occurs through target site modification by methylation or by upregulated efflux encoded by erm or mef genes, by amino acid changes to trimethoprim-sulfamethoxazole, by decreased permeability, efflux pumps and alteration of

enzymes, and by inactivating enzymes to chloramphenicol. Currently, the increase in multidrug-resistant *S. pneumoniae* strains has been reported from many countries, including isolates from both clinical cases and carriers (Fair and Tor 2014; Velasquez et al. 2009). In the medical literature, a significant increase in otitis media prevalence caused by multidrug-resistant *S. pneumoniae* is actively discussed (Taneja and Taneja 2014). The patients remain infectious for a longer time because antimicrobial resistance reduces the effectiveness of treatment. It increases the risk of spreading resistant microorganisms to others. The rapid spreading of multidrug-resistant *S. pneumoniae* is a serious concern for the primary care providers who treat AOM in children (Xu et al. 2009). Furthermore, the empirical antibiotics used to treat of infections caused by multidrug-resistant organisms rises health care expenses and generates several adverse effects, including selection of antibiotic-resistant mutants (Parra et al. 2004). Genetic studies show that resistance to penicillins, cephalosporins, and some other antibiotics spread by accumulation of point mutations in the associated chromosomal genes in commensal species such as *Streptococcus oralis* and *Streptococcus mitis*, which serve as a genetic source for *S. pneumoniae* (Kilian 2012).

The prevalence of moderately penicillin-resistant strains changes from country to country and almost for all countries there is an increase in the prevalence of moderately resistant and highly resistant strains (Cartwright 2005). In the studies related to penicillin resistance of *S. pneumoniae* in healthy children in our country were determined resistances to penicillin between 17.9-33.9% (Enginyurt et al. 2016). Penicillin-resistant clones (serotypes 6A, 6B, 9V, 14, 19F, 23F) which have been spreading to several countries were responsible for most of these multidrug-resistant strains. After the introduction in 2000 of the 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7) in the United States, the incidence of pneumococcal disease caused by vaccine serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) decreased significantly among children. But, rates of pneumococcal disease caused by non-vaccine serotypes, including drug-resistant strains, particularly serotype 19A, increased. Serotype 19A is a high among multi-drug resistant strains (Nuorti et al. 2010).

Our *S. pneumoniae* strain was high-level resistant to penicillin. The serotype of the *S. pneumoniae* strain was determined as 19A and the sequence type was found ST199. It was a multidrug-resistant strain, and it was resistant to amoxicillin-clavulanic acid, erythromycin, trimethoprim-sulfamethoxazole, tetracycline, clindamycin. In a report (reviewed from the Drug-Resistant *S. pneumoniae* Therapeutic Working Group guidelines and the other articles identified from the data sources) that provide consensus recommendations for the management of AOM, amoxicillin at conventional (40-45mg/kg) or high doses (80-90 mg/kg/day) remains an appropriate choice for first-line therapy for AOM caused by drug-resistant multidrug-resistant *S. pneumoniae*. For patients with clinically defined treatment failure with amoxicillin, appropriate options for second-line therapy include high-dose amoxicillin/clavulanate (90 mg/kg/day) and ceftriaxone. Ceftriaxone should be used cautiously and reserved for patients with especially severe infections according to this report (Hoberman et al. 2002).

In our case, the patient had received many times different antibiotics, including cefuroxime, and were started on intravenous ceftriaxone (100 mg/kg/day) and vancomycin (15 mg/kg/every 12h) for a period of 4 days, with by aspiration, due to the failure of previous treatment. The patient responded well to treatment and a great clinical improvement was recorded. The choice of antibiotic and dosage is recommended according to the findings of local antibacterial susceptibility studies, in order to achieve the optimum drug efficacy and avoid resistance (Parra et al. 2004). As a result, these case report was evaluated in order to draw attention to the increase of pneumococcal AOM infections with multi-drug resistant in among children.

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