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Meningitis with vancomycin-tolerant Streptococcus pneumonia: a case report in the northeast of Iran

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ABSTRACT

Meningitis is a clinical syndrome that occurs for a variety of reasons such as bacterial infections. Acute bacterial meningitis can occur at any age, and is a leading cause of mortality worldwide. Streptococcus pneumonia is a bacterial meningitis that can lead to pneumococcal meningitis, especially in children. In recent decades, the percentage of pneumococcal strains resistant to penicillin and cephalosporins isolated from children has increased. This has made vancomycin the first empirical antibiotic therapy for children with suspected bacterial meningitis.

In this report, we introduce a 13-month-old child who was brought to the emergency department of Akbar Children's Hospital, Mashhad (a city in northeastern Iran) with complaints of high-grade fever and drowsiness. Meningitis was diagnosed via sampling of cerebrospinal fluid, and the culture indicated S. pneumonia that was non-sensitive to vancomycin. The e-test and microdilution have been approved to determine the minimum inhibitory concentration (MIC) of vancomycin; however, the e-test is a more straightforward method and the error probability is less while providing similar results to microdilution. Also, both methods can predict vancomycin tolerance or reduce sensitivity to vancomycin. Results of the e-test indicate MIC=2.

Keyword: Bacterial meningitis, empiric therapy, pneumococcal meningitis, vancomycin tolerant Streptococcus pneumonia.

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Introduction

Meningitis is a clinical syndrome characterized by inflammation of the meningeal membrane covering the mucosa and spinal cord. Meningitis occurs for a variety of reasons, such as infectious causes (bacterial, viral, fungal), autoimmune diseases, cancer, or drug reactions (1). Acute bacterial meningitis, a common type of bacterial meningitis, is a severe, fatal inflammation of the meninges and subarachnoid space caused by bacteria that can occur at any age, and is a major cause of morbidity and mortality (ranging from 19% to 26%), globally (2-4). Streptococcus pneumonia causes approximately 70% of cases of bacterial meningitis with a high mortality and morbidity rate (5). What is more, pneumococcal meningitis is the most common cause of bacterial meningitis in Europe and the United States (6). In the last few decades, the percentage of pneumococcal strains that are

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not sensitive to penicillin and cephalosporin has increased (7). Hence, patients infected with these bacteria require immediate care and treatment because inflammation in the protective membranes covering the brain and spinal cord could cause vasospasms and possible thrombosis of blood and brain vessels, as well as possible blockage of cerebral vessels. Also, inflammatory products of bacteria and neutrophils can cause nerve necrosis (3). Therefore, due to the importance of time in the treatment of this infection and the reduction of its possible dangerous complications, as well as due to the emergence of strains resistant to penicillin and cephalosporins, the use of vancomycin in the experimental treatment of children suspected of bacterial meningitis is recommended (8).

Of course, indiscriminate use of this drug may cause the development of resistance and tolerance of bacteria to this critical drug. Recent reports indicate that the growth of strains of pneumococcus have been halted in the presence of vancomycin; however, they have not been totally destroyed, and they have probably become tolerant to the presence of this drug.

Pneumococcal strains resistant to vancomycin or beta-lactam are challenging to eradicate from the meninges, so finding these strains will have significant implications in treating pneumococcal meningitis (9). The gold standard for diagnosing bacterial meningitis is still a cerebrospinal fluid (CSF) culture. However, the use of antibiotics to treat before culture will result in a negative culture (10).

In recent decades, the percentage of pneumococcal strains isolated from children resistant to penicillin (2,4) and cephalosporins has increased. Increased strains resistant to standard drugs have made vancomycin the first experimental antibiotic treatment for children with suspected bacterial meningitis. Increased use of vancomycin has also led to developing resistance or tolerance to this drug (2,4,9).

In this case report, we describe the characteristics of a vancomycin-tolerant pneumococcus strain isolated from the cerebrospinal fluid of a 13-month-old child with meningitis. The treatment of this child started with vancomycin, which did not respond to the treatment after three days, and the patient still had a persistent fever.

Case report

A 13-month-old male with high-grade fever and lethargy was referred to Akbar Children's Hospital in April 2020 with symptoms of meningitis. CSF and blood samples were tested in a laboratory. In addition, the patient underwent two lumbar punctures (LP).

CSF analysis at the time of admission showed a white blood cell (WBC) count of 322 cells/mL (90% polymorphonuclear cells) and a Gram stain showing Gram-positive cocci in pairs and chains. CSF protein and glucose were 176 and 73 mg/dL, respectively. After LP, treatment with vancomycin 60 mg/kg/divided every six hours, ceftriaxone 100 mg/kg divided every 12 hours, and dexamethasone was started. On the third day of treatment, his condition did not improve, and high-grade fever and lethargy continued, so the second LP was done. The CSF had a WBC count of 2100 cells/mL (76% polymorphonuclear cells and 24% lymphocytes).

CSF protein and glucose were 96 and 75 mg/dL, respectively. CSF was cultured on blood agar, chocolate agar, and eosin methylene blue (EMB). S. pneumoniae was detected by bile solubility tests and optochin sensitivity tests. Antibiotic susceptibility testing for this bacterium was performed via the Kirby-Bauer disk diffusion assay (resistant: cotrimoxazole, cefoxitin, erythromycin, clindamycin, azithromycin; sensitive: gentamicin high level, 120 µg). Due to its resistance to beta-lactams, a e-test was performed for vancomycin (MIC=2).

The strain in the vancomycin MIC test, which showed a MIC ≥1.5 µg/ml, was considered to be decreased susceptibility to vancomycin or tolerant to vancomycin (11).

Tolerance or resistance to vancomycin can be determined if we have a ratio of MBC/MIC. After obtaining permission from the parents of the patient, we added linezolid twice a day at the rate of 10 mg/kg to the treatment regimen. The clinical response was observed one day after starting the new treatment. Clinical findings improved, fever decreased, and the child's appetite improved.

After 14 days of treatment with linezolid, ESR decreased, CRP level reached 0.1 and hematological findings were normal. S.pneumoniae isolated from the patient's cerebrospinal fluid appeared to be tolerant to vancomycin. If this strain was vancomycin-resistant, it would not grow in a culture medium. Therefore, the isolated strain was reported to be insensitive to vancomycin.

Furthermore, linezolid is a suitable treatment candidate for pneumococcal meningitis due to its effect on penicillin-resistant isolates of S.pneumoniae and its penetration into the cerebrospinal fluid (CSF) regardless of the presence of inflammation in the meninges (11, 12).

Discussion

The incidence of antibiotic resistance in S. pneumoniae has increased dramatically in recent decades, and even strains resistant to multiple antibiotics have been reported worldwide (13,14). As of 2004, no vancomycin-resistant pneumococci were reported, so vancomycin was

added to standard meningitis treatment (15), and is now recommended for the initial treatment of pneumococcal meningitis in children (16, 17).

Lack of sensitivity to vancomycin may be due to vancomycin-resistance or increased tolerance to this antibiotic. The presence of S. pneumoniae clinical isolates that are not sensitive to vancomycin has raised many concerns (18).

Eradication of such strains is also challenging and requires long-term antibiotic use, especially in the meninges, which have a weak host defense (9). Antimicrobial tolerance is defined as the capacity of bacteria to survive but not grow in the presence of antibiotics (2,19).

Bacteria do not produce or lyse under conditions of intolerance to an antibiotic. This mechanism is different from resistance to a drug (20, 21). Bacteria that have become tolerant to a drug can reproduce again by removing the drug. Therefore, tolerance to antimicrobial agents may lead to antibiotic treatment failure (21,22).

The advent of vancomycin-tolerant S. pneumoniae (VTSP) could severely limit the treatment options for S. pneumonia (2). McCullers et al. published the first report of vancomycin tolerance in S. pneumoniae. His study states that because vancomycin-tolerance is associated with clinical failure in the treatment of pneumococcal meningitis, increased surveillance for resistant strains of organisms is suggested. In another case report from Turkey, a six-month-old child, who was diagnosed with pneumococcal meningitis and did not respond to the usual treatments, was administered vancomycin. However, when lysolide was added to the treatment modality, symptoms improved (23).

In Memphis, Tennessee, an isolate of S. pneumoniae was isolated from the cerebrospinal fluid of a 10-month- old child who was tolerant to vancomycin. After investigation, the Tupelo strain was confirmed. The study emphasizes that tolerance of a phenotype will cause resistance, and may cause the clinical failure of antibiotic treatment (9).

Determination of vancomycin-tolerance is based on detailed empirical studies but is complex and not commonly performed in all medical diagnostic laboratories. Clinical laboratories cannot easily detect antibiotic-tolerant strains unless they determine the MBC to MIC ratio. However, the e-test and microdilution methods for determining vancomycin MIC are easily performed, and the results are consistent. These two tests can predict vancomycin-tolerance or decreased sensitivity to vancomycin (24).

We added linezolid to our antibiotic regime after finding a poor response to the use of vancomycin only. Linezolid could be used alone or in combination with vancomycin nonsusceptibility isolates of S. pneumonia (19). Hence, linezolid seems to be a suitable alternative for treating pneumococcal meningitis resistant to vancomycin (25).

Conclusion

The findings of this study are important because it brings attention to the possible gobal emergence of S. pneumonia strains resistant to vancomycin, granted such cases are presently rare.

It is probable that the increased use of vancomycin in meningitis to treat strains resistant to penicillin or cephalosporins may be contributing to the development of resistant isolates; therefore, linezolid can be used alone or in combination with vancomycin-resistant isolates of S. pneumoniae.

In addition, since vancomycin-tolerance is associated with clinical treatment failure, it is suggested more attention be giving to find drug-tolerant isolates and more studies should be done on the mechanisms of this phenomenon. Furthermore, the e-test and microdilution, to easily determine the minimum inhibitory concentration of vancomycin, could predict vancomycin tolerance or decreased vancomycin sensitivity; thus, possibly improving treatment and care and reducing mortality rates. However, more studies are needed.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article's research, authorship, and publication. Inform consent was obtained for this publication. The authors have no intent to profit financially from this publication.

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