Meningitis in a Canadian adult due to high level penicillin-resistant, cefotaxime-intermediate *Streptococcus pneumoniae*

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C TREMBLAY, A-M BOURGAULT, P ST-ANTOINE. Meningitis in a Canadian adult due to high level penicillin-resistant, cefotaxime-intermediate *Streptococcus pneumoniae*. *Can J Infect Dis* 1996;7(3):205-207. Invasive penicillin-resistant pneumococcal (PRSP) infections are increasing worldwide. In Canada, the incidence of penicillin resistance among *Streptococcus pneumoniae* isolates is estimated at greater than 6%. In Quebec, only one case of PRSP meningitis has been reported and involved an infant. An adult patient is described who presented with meningitis caused by high level penicillin-resistant, cefotaxime-intermediate *S pneumoniae*.

Key Words: Meningitis, Penicillin-resistant pneumococci, *Streptococcus pneumoniae*

Cas de méningite causée par une souche de *Streptococcus pneumoniae* très résistante à la pénicilline et moyennement résistante au céfotaxime chez un adulte canadien

RÉSUMÉ : Les infections invasives dues à des pneumocoques résistants à la pénicilline sont en hausse partout dans le monde. Au Canada, l'incidence d'isolats de *Streptococcus pneumoniae* pénicillino-résistants est estimée à plus de 6 %. Au Québec, un seul cas de méningite attribuable à un tel organisme pathogène a été signalé chez un nourrisson. Le cas décrit ici est celui d'un patient adulte atteint de méningite causée par une souche de *S. pneumoniae* très résistante à la pénicilline et moyennement résistante aux céfotaxime.

Infections due to *Streptococcus pneumoniae* continue to be a significant cause of morbidity and mortality (1). Penicillin is still considered the drug of choice for the treatment of these infections (2). However, several reports have documented the increasing penicillin resistance of *S pneumoniae* worldwide (1,3). In Canada, only a few cases of serious pneumococcal disease caused by strains with reduced susceptibilities to penicillin have been reported (4-8). We describe a Canadian

adult with pneumococcal meningitis caused by a high level penicillin-resistant *S pneumoniae* (minimal inhibitory concentration [MIC] greater than 2 mg/L).

CASE PRESENTATION

A 48-year-old female was brought to the hospital because of fever and altered consciousness. The patient had been well and working regularly as a bank clerk until the day of her ad-

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mission. Early that day, she complained of an acute right ear-ache, nausea, fever and chills. Her condition worsened rapidly. The patient was brought to her community hospital the following night (March 15, 1995) because of altered consciousness. The patient had experienced several episodes of otitis in childhood but had no other significant medical history.

On examination, the patient was stuporous. Pulse was 120 beats/min, blood pressure 120/70 mmHg, respirations 24/min and temperature 39.8°C. Examination of the head and neck was notable for marked nuchal rigidity. Neurological examination revealed a stuporous woman who moved all four limbs equally and withdrew to painful stimulus. No focal neurological deficits or cranial nerve abnormalities were discernable. The remainder of the physical examination was normal.

Lumbar puncture yielded cloudy cerebrospinal fluid (CSF) with 0.02×10^{12} erythrocytes and 14.5×10^9 leukocytes/mm³ (97% polymorphonuclear cells), glucose 0.1 mmol/L (normal range 2.2 to 3.9) and protein 4.4 g/L (0.15 to 0.45). Gram stain of spinal fluid revealed the presence of Gram-positive diplococci. Therapy with penicillin G 24 million U/day was begun immediately after lumbar puncture on the first hospital day. *S pneumoniae* was isolated from the blood and the CSF. Combination therapy with vancomycin 2 g/day and cefotaxime 9g/day was substituted 32 h after admission when initial susceptibility results performed on the isolate showed that the *S pneumoniae* was resistant to the 1 µg oxacillin disk.

At her family's request, the patient was transferred to the authors' institution on the evening of the third hospital day (March 17, 1995). She was intubated before transportation to protect her airways. On admission, she was still stuporous but moved all limbs spontaneously. Computed tomography (CT) of the head did not reveal any intracranial lesions but showed images compatible with mild bilateral maxillary and ethmoidal sinusitis. On March 19, the lumbar puncture was repeated. Examination of the slightly cloudy fluid revealed the following results: 0.00061×10^{12} erythrocytes, 0.132×10^9 leukocytes (58% polymorphonuclear), protein 1.37 g/L and glucose 4.9 mmol/L. The Gram stain was negative but six colonies of *S pneumoniae* grew on chocolate agar plate. By the following day, the patient had become more alert, fever was down to 38°C and nuchal rigidity was improved. The lumbar puncture was repeated on March 22. The spinal fluid was clear and results of analyses were as follows: 0.071×10^9 leukocytes (25% neutrophils), glucose 2.4 mmol/L, protein 1.04 g/L and negative culture. The patient's overall condition continued to improve over the next several days with complete recovery of consciousness. However, on March 23, the fever rose to 39°C and the patient had an episode suggestive of a seizure. A repeat CT scan of the head, glucoheptonate cerebral scintigraphy and electroencephalography did not reveal any focal lesions. A CT scan of the mastoids showed signs of chronic inflammation. An ear, nose and throat evaluation confirmed the presence of hypoacusia of the left ear attributed to old middle ear infections. There were no signs of acute otitis or mastoiditis. The fever persisted and a rash developed on March 27. On March 28, cefotaxime and vancomycin were stopped because of these cutaneous manifestations and imipenem was substi-

tuted to complete 21 days of antibiotic therapy. The patient recuperated completely, the fever abated and she was discharged home.

MICROBIOLOGY

Blood culture and CSF isolates of *S pneumoniae* were identified according to standard methods. Susceptibility testing was performed by the microbroth dilution method as described in National Committee for Clinical Laboratory Standards (NCCLS) standard M7-A3 (9).

The MICs as determined by the NCCLS broth microdilution method were 2 mg/L for penicillin G, 1 mg/L for cefotaxime and 0.12 mg/L for imipenem. The *S pneumoniae* isolate belonged to serogroup 9 (National Centre for Streptococci, Edmonton, Alberta).

DISCUSSION

In the United States, the incidence of pneumococcal meningitis is estimated at 1.1/100,000 population with a case fatality rate of 19% (2). In spite of appropriate treatment, 30% of patients suffer from long term disabilities, mainly hearing loss. Until recently, penicillin has been the antimicrobial agent of choice for the treatment of pneumococcal meningitis. However, empirical treatment for these infections may have to be modified.

Surveillance data from the Centers for Diseases Control and Prevention in Atlanta, Georgia have shown that high level resistance to penicillin has increased more than 60-fold in the past decade, from 0.02% during the period 1979–87, to 1.3% in 1992 (10). A study done in Toronto found the prevalence of penicillin-resistant pneumococci (PRSP) at 7.3% with high-level resistance estimated at 1.9% in 1993–94 (4), a marked increase compared with results obtained in a 1988 study (11). Previous data for Quebec have indicated a prevalence of less than 4% for these strains (12), and it may be increasing (13). In Canada, only a few cases of serious pneumococcal disease caused by strains with reduced susceptibilities to penicillin have been reported. Three Canadian reports on serious infections caused by high-level penicillin-resistant *S pneumoniae* have involved two infants and one five-year-old child (5–7).

The management of PRSP meningitis is becoming increasingly difficult. Some PRSP are also resistant or intermediate (MIC 1 mg/L) to the extended spectrum cephalosporins commonly used for the empirical therapy of meningitis, with treatment failures reported (1,14,15). Cephalosporins and vancomycin serve as alternative therapeutic agents in infections with pneumococcal isolates intermediate or resistant to penicillin (1,14,16,17). Vancomycin should be added when highly resistant strains are suspected or isolated. Our patient was initially treated with penicillin, and therapy with cefotaxime and vancomycin was substituted 32 h later when the initial susceptibility report indicated resistance to the oxacillin disk. She fortunately recovered completely. This clearly establishes the importance of rapid susceptibility testing methods. In view of the recent surveillance data, however, initial empirical therapy with vancomycin and a third-generation

cephalosporin (cefotaxime or ceftriaxone) would have been optimal.

It is recommended that the response of any patient with PRSP meningitis be monitored by repeat examination and culture of the CSF because vancomycin treatment failures have been reported (1,15,16). Possible explanations for treatment failures include the use of a low dose of vancomycin, highly variable vancomycin concentration in the CSF and the concomitant use of dexamethasone (16). In the event that the patient's clinical condition has worsened or that the follow-up CSF examination is unsatisfactory, it is recommended that the treatment be modified based on in vitro susceptibility results. Alternative therapeutic options include rifampin, chloramphenicol if the minimal bactericidal concentration is less than 4 mg/L, and imipenem, although it has the potential risk of drug-related seizures (1,16). Our patient's second CSF specimen was still culture-positive after 48 h of cefotaxime and vancomycin treatment but there were definite improvements in cytology and biochemical markers and a significant reduction in the number of organisms.

A wide variety of serotypes have been associated with re-

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