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

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CASE REPORT

**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 admission. She presented with fever, headache, and altered mental status. Physical examination revealed meningismus and reduced neck stiffness. Lumbar puncture revealed a cloudy cerebrospinal fluid with increased white blood cell count and elevated protein levels. Ceftriaxone and vancomycin were initiated empirically. Blood cultures grew *Streptococcus pneumoniae* with a high level of penicillin resistance (minimal inhibitory concentration [MIC] greater than 2 mg/L).

**CASE DISCUSSION**

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).

**Key Words:** Meningitis, Penicillin-resistant pneumococci, *Streptococcus pneumoniae*
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 fol-
lowing night (March 15, 1995) because of altered conscious-
ness. 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 exami-
nation revealed a stuporous woman who moved all four limbs
equally and withdrew to painful stimulus. No focal neurologi-
cal deficits or cranial nerve abnormalities were discernable.
The remainder of the physical examination was normal.

Lumbar puncture yielded cloudy cerebrospinal fluid (CSF)
with 0.02x10^{12} erythrocytes and 14.5x10^9 leukocytes/mm^3
(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 diplo-
cocci. 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. Com-
bination therapy with vancomycin 2 g/day and cefotaxime
9g/day was substituted 32 h after admission when initial sus-
ceptibility 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 ethmoi-
dal sinusitis. On March 19, the lumbar puncture was repeated.
Examination of the slightly cloudy fluid revealed the follow-
ing results: 0.00061x10^{12} erythrocytes, 0.152x10^9 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 re-
sults of analyses were as follows: 0.071x10^9 leukocytes (25%
neutrophils), glucose 2.4 mmol/L, protein 1.04 g/L and nega-
tive culture. The patient’s overall condition continued to im-
prove 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 re-
peat CT scan of the head, glucoseheptonate cerebral scintigra-
phy and electroencephalography did not reveal any focal
lesions. A CT scan of the mastoids showed signs of chronic in-
flammation. An ear, nose and throat evaluation confirmed the
presence of hypoacousia of the left ear attributed to old middle
ear infections. There were no signs of acute otitis or mastoidi-
tis. 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 re-
cuperated completely, the fever abated and she was disch-
germed home.

**MICROBIOLOGY**

Blood culture and CSF isolates of S pneumoniae were iden-
tified according to standard methods. Susceptibility testing
was performed by the microbroth dilution method as de-
scribed in National Committee for Clinical Laboratory Stan-
dards (NCCLS) standard M7-A5 (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 be-
longed to serogroup 9 (National Centre for Streptococci, Ed-
monton, Alberta).

**DISCUSSION**

In the United States, the incidence of pneumococcal menin-
gitis is estimated at 1.1/100,000 population with a case fatal-
ity 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 re-
sistance 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 in-
crease 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 infec-
tions 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 increas-
ingly difficult. Some PRSP are also resistant or intermediate
(MIC 1 mg/L) to the extended spectrum cephalosporins com-
monly used for the empirical therapy of meningitis, with treat-
ment failures reported (1,14,15). Cephalosporins and
vancomycin serve as alternative therapeutic agents in infec-
tions 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 cefo-
taxime and vancomycin was substituted 32 h later when the
initial susceptibility report indicated resistance to the oxacil-
lin disk. She fortunately recovered completely. This clearly es-
tablishes the importance of rapid susceptibility testing
methods. In view of the recent surveillance data, however, ini-
tial 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 resistant isolates, including 6B, 23F, 14, 9V, 19A, 19F, and for some of these, studies have provided evidence for intercontinental spread of drug-resistant clones (10). Of interest, all these serotypes are included in the available 23-valent vaccine. Although pneumococcal immunization could prevent serious infections, used according to the actual guidelines (18), the vaccine would not have been administered to our patient.

CONCLUSIONS

The prevalence of penicillin and cephalosporin-resistant strains of S pneumoniae is low in Canada but increasing. The present case of meningitis in an adult caused by a highly penicillin-resistant, cefotaxime-intermediate S pneumoniae emphasizes the importance of rapid and accurate susceptibility testing methods and results, and continued surveillance of resistance patterns for both penicillin and third-generation cephalosporins. The emergence of penicillin-resistant S pneumoniae has major clinical and public health implications. At present, vancomycin and cefotaxime or ceftriaxone should be prescribed as initial empirical therapy for suspected pneumococcal meningitis.

References

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