Journal of Global Antimicrobial Resistance 11 (2017) 188–189

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Letter to the Editor

First report of ceftriaxone-resistant *Streptococcus pneumoniae* meningitis in Belarus

Sir,

Streptococcus pneumoniae is the leading agent of bacterial meningitis in adult patients in developed countries [1]. Multidrug-resistant (MDR) pneumococcal strains are a growing problem for empirical antibacterial therapy in invasive, often life-threatening, infections.

Here we report the case of a 54-year-old man who was admitted to the intensive care unit (ICU) of Minsk City Hospital of Infectious Diseases (Minsk, Belarus) in April 2015 because of fever, severe headache, nausea, vomiting and altered consciousness. On examination, he had a temperature of 40 °C, a respiratory rate of 22 breaths/min with normal oxygen saturation, a heart rate of 110 beats/min and his blood pressure was 150/90 mm Hg. Cardiac, lung and abdominal examinations revealed no pathology. Neck stiffness and Kernig's symptom were clearly pronounced. The Glasgow Coma Scale (GCS) was 12. The cranial nerves were intact.

One month prior to the onset of fever the patient had facial pain in the projection of the maxillary sinuses but did not seek medical attention. He had not received any systemic antibiotics during the previous 3 months. His past medical history was unremarkable. The patient's relatives reported the fact of alcohol abuse for the last 3 years.

On admission, blood examination revealed leucocytosis (24 500 cells/mL; normal range 4000–9000 cells/mL) and an increased C-reactive protein level (36 IU/L; normal <6 IU/L). Cerebrospinal fluid (CSF) analyses showed a white blood cell (WBC) count of 3904 WBC/mL (95% neutrophils, 5% lymphocytes) (normal range <5 WBC/mL), glucose concentration 3.1 mmol/L (normal range 2.2–3.8 mmol/L) and protein concentration 1.0 g/L (normal range 0.15–0.45 g/L). Treatment with meropenem 2.0 g three times daily and dexamethasone 10 mg every 6 h was started pending laboratory results.

CSF-PCR was positive for *S. pneumoniae* DNA and 40 h later CSF culture grew a MDR *S. pneumoniae* strain (BLR/CSF/385/2015). According to the susceptibility of the micro-organism, moxifloxacin 400 mg once daily was added.

Radiography of the paranasal sinuses revealed bilateral levels of fluids. Following puncture of the maxillary sinus, pus was obtained. The patient was transferred to a multidisciplinary hospital where surgical revision of the maxillary sinuses was performed.

Two days later the patient's fever decreased and he experienced significant improvement. After the full 14-day-course of antibacterial therapy, he was discharged completely recovered.

Investigations in the National Reference Laboratory for Invasive Bacterial Diseases (Minsk, Belarus) confirmed the identification result (growth of distinctive α-haemolytic colonies on blood agar, morphology of Gram-positive diplococcus, negative catalase test, optochin susceptibility, bile solubility and positive autolysin real-time PCR detection). The resistance phenotype of strain BLR/CSF/385/2015 was verified by antimicrobial susceptibility testing (Table 1). Minimum inhibitory concentrations (MICs) were determined by the broth microdilution reference method using cation-adjusted Mueller–Hinton broth (Sigma-Aldrich, St Louis, MO) with 5% lysed horse blood (prepared in-house) according to Clinical and Laboratory Standards Institute (CLSI) methodology (document M07-A10). Susceptibility interpretation was performed according to CLSI 2017 interpretive criteria (document M100, 27th ed.).

Molecular typing using the multiplex conventional PCR protocol of the US Centers for Disease Control and Prevention (CDC) showed that the strain belonged to serotype 19F. Detection of antibiotic resistance determinants for β-lactams and macrolides in conventional multiplex PCR demonstrated the presence of *mefA* (macrolide efflux protein A) and *ermB* (macrolide target-modifying RNA methylase) genes as well as alterations in the penicillin-binding protein genes *pbp1a* (four consecutive substitutions: 574T → N, 575S → T, 576Q → G and 577F → Y) and *pbp2x* (338T → A mutation in the 337STMK motif) and the absence of specific modifications in *pbp2b* (431T → K and 432Q → L substitutions close to the conserved motif 448SSN).

Multilocus sequence typing (MLST) analysis showed that the described strain belongs to ST320, related to international clone CC320/271, characterised worldwide by a high proportion of MDR and extensively drug-resistant (XDR) serogroup 19 strains with high-level resistance to β-lactams, including third-generation cephalosporins (ceftriaxone MICs 2–8 mg/L) [2]. Usually, MDR 19F serotype strains belong to ST271 or ST236 (Taiwan^{19F}-14 pre-PCV7 era variant), whereas 19A serotype strains belong to ST320 (post-PCV7 clone, which have been formed like a double-locus variant of the described Taiwan^{19F}-14 clone and because of PCV7 vaccination selective pressure through serotype switching). However, strains with such a rare combination of genotypic (ST320) and phenotypic (19F serotype, ceftriaxone MIC of 2 mg/L) characteristics have previously been isolated in Poland and Canada, but the significance of their origin remains unclear.

Potential risk factors of MDR *S. pneumoniae* meningitis in adults are paediatric serotypes, older age, human immunodeficiency virus (HIV) infection, immunosuppression, previous antibiotic use, previous hospital admission, attending day care and living in an urban area [3,4]. The age of the patient reported here, immunosuppression due to alcohol abuse, the urban location and 19F *S. pneumoniae* serotype are possible risk factors for MDR invasive pneumococcal infection.

http://dx.doi.org/10.1016/j.jgar.2017.09.003

Table 1
Antimicrobial susceptibility testing results for the multidrug-resistant *Streptococcus pneumoniae* strain BLR/CSF/385/2015.

Antimicrobial agent	MIC (mg/L) [Interpretation]	CLSI breakpoints (S/R)
Benzylpenicillin	4 [R]	≤0.06/≥0.125
Ampicillin	8	N/A
Amoxicillin	8	N/A
Cefuroxime	16	N/A
Cefotaxime	2 [R]	≤0.5/≥2
Ceftriaxone	2 [R]	≤0.5/≥2
Cefepime	2 [R]	≤0.5/≥2
Meropenem	1 [R]	≤0.25/≥1
Ertapenem	2	N/A
Levofloxacin	1 [S]	≤2/≥8
Moxifloxacin	0.125 [S]	≤1/≥4
Ofloxacin	2 [S]	≤2/≥8
Sparfloxacin	0.25	N/A
Vancomycin	0.5 [S]	≤1/–
Erythromycin	≥512 [R]	≤0.25/≥1
Clindamycin	128 [R]	≤0.25/≥1
Tetracycline	16 [R]	≤1/≥4
Doxycycline	4 [R]	≤0.25/≥1
Linezolid	0.5 [S]	≤2/–
Chloramphenicol	4 [S]	≤4/≥8
Rifampicin	0.064 [S]	≤1/≥4
SXT[a]	16 (304) [R]	≤0.5 (9.5)/≥4 (76)

MIC, minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute; S, susceptible; R, resistant; N/A, not available; SXT, trimethoprim/sulfamethoxazole.

[a] Trimethoprim/sulfamethoxazole (SXT) in the ratio 1:19. Breakpoints are the trimethoprim concentration (with the sulfamethoxazole concentration in parenthesis).

Currently, third-generation cephalosporins are the mainstay agents for the empirical treatment of invasive pneumococcal infections. Although Belarus is usually considered a country with a low prevalence of MDR *S. pneumoniae* strains and without a tendency for the wide circulation of penicillin-resistant strains [5], this case demonstrates the need for high clinical suspicion in adults with community-acquired meningitis who do not respond to traditional antibacterial therapy.

The emergence of MDR ceftriaxone-resistant invasive pneumococci belonging to the international clonal complexes requires the functioning of a qualitative microbiological surveillance system in Belarus, especially before the introduction of PCV mass immunisation.

Funding

None.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016;22(Suppl. 3):S37–62.
[2] Golden AR, Rosenthal M, Fultz B, Nichol KA, Adam HJ, Gilmour MW, et al. Characterization of MDR and XDR *Streptococcus pneumoniae* in Canada, 2007–13. J Antimicrob Chemother 2015;70:2199–202.
[3] Crowther-Gibson P, Cohen C, Klugman KP, de Gouveia L, von Gottberg A. Group for Enteric, Respiratory, and Meningeal Disease Surveillance in South Africa (GERMS-SA). Risk factors for multidrug-resistant invasive pneumococcal disease in South Africa, a setting with high HIV prevalence, in the prevaccine era from 2003 to 2008. Antimicrob Agents Chemother 2012;56:5088–95.
[4] Kim L, McGee L, Tomczyk S, Beall B. Biological and epidemiological features of antibiotic-resistant *Streptococcus pneumoniae* in pre- and post-conjugate vaccine eras: a United States perspective. Clin Microbiol Rev 2016;29:525–52.
[5] Karpov I, Kachanka A. Nasopharyngeal carriage and antimicrobial resistance in isolates of *Streptococcus pneumoniae* in Belarus. 26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). Basel, Switzerland: ESCMID; 2016.

Alexander Davydov
Mikita Salavei
Leonid Titov
Igor Karpov*

Department of Microbiology, Virology and Immunology, Belarusian State Medical University, Minsk, Belarus

Laboratory for Clinical and Experimental Microbiology, The Republican Research and Practical Center for Epidemiology and Microbiology, Minsk, Belarus

Department of Infectious Diseases, Belarusian State Medical University, Minsk, Belarus

Laboratory for Clinical and Experimental Microbiology, The Republican Research and Practical Center for Epidemiology and Microbiology, Minsk, Belarus

Department of Infectious Diseases, Belarusian State Medical University, Minsk, Belarus

* Corresponding author.
E-mail address: igorkarpov57@mail.ru (I. Karpov).

Received 5 August 2017

Available online 9 September 2017