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한국에서 광역내성 *Salmonella* Typhi 첫 증례

The First Case of Extensively Drug-resistant *Salmonella* Typhi in South Korea

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Dear Editor,

Typhoid fever, caused by *Salmonella enterica* subsp. *enterica* serovar Typhi (*S.* Typhi), is one of the serious bloodstream infections that belongs to the class 2 of the legal infectious diseases in Korea. It has variable incubation period ranging from one to six weeks depending on the infectious dose [1, 2] and requires urgent treatment with antimicrobial agents. However, recently, the prevalence of *S.* Typhi strains resistant to antimicrobial agents has been gradually increasing [3, 4]. This fact poses the failure of empirical treatment or a threat to the control of infectious typhoid fever [3]. In Korea, about 100-200 cases of typhoid are reported annually. To our knowledge, we report the first case of extensively drug-resistant (XDR) *S.* Typhi in Korea. Patient demographic and clinical information was collected from Sangju Red Cross Hospital (Sangju, Korea) by formally applying for access to the medical records of the outsiders and the informed consent from the patient. This study was exempted by the Institution Review Board of Kyungpook National University Chilgok Hospital (Reference number: KNUCH 2019-04-015).

A 28-year-old male patient having fever and cough for a day visited the emergency department on the next day. He was found negative for the influenza antigen test and was discharged with a three-day prescription of cefdinir. After three days, he visited the emergency department again with the same symptoms and worsening diarrhea. Therefore, the treatment was switched to amoxicillin and a β-lactamase inhibitor. However, due to uncontrolled fever and significantly worsened diarrhea, he was hospitalized. Chest X-ray and abdomen CT scan were unremarkable except an evidence of probable mesenteric lymphadenitis. Therefore, he was treated with ceftriaxone for five days; however, his symptoms did not improve. Although his history was unremarkable, the symptoms began in 26 days after his arrival in Korea from a visit to Pakistan. AST, ALT, and ALP were moderately increased, but all the viral hepatitis markers were negative. Stool culture for *Salmonella* spp., *Shigella* spp., *Vibrio* spp., and *Clostridium difficile* showed negative until discharge. The toxin A and B assay for *C. difficile* was negative. However, blood culture revealed positive and *Salmonella* ser. Typhi was identified by using the Vitek2 Gram-negative identification system (bioMérieux, Durham, NC, USA). Serotyping for *Salmonella* spp. by serum agglutination test using *Salmonella* antisera (Joongkyeom, Goyang, Republic of Korea) revealed group D. However, anti-microbial susceptibility tests showed MICs for ampicillin, trimethoprim/sulfamethoxazole, and cefotaxime at ≥32 μg/mL, ≥320 μg/mL, and ≥64 μg/mL, respectively, using the Vitek2 AST-N224 system (bioMérieux) and for ciprofloxacin at ≥2 μg/mL by the manual microdilution, according to the

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CLSI guidelines [5]. Therefore, it was strongly suspected to be an XDR *S.* Typhi strain, which was resistant to three first-line antibacterial agents (chloramphenicol, ampicillin, and trimethoprim/sulfamethoxazole) as well as fluoroquinolones and third-generation cephalosporins. The isolate confirmed as *Salmonella enterica* subsp. *enterica* Ty2 through the 16S rRNA sequencing (Identities=1,384/1,385, 99.93%). The $bla_{CTX\text{-}M\text{-}15}$ extended-spectrum β-lactamase (ESBL) gene and a single mutation in *gyrA* (S83F) were detected. His symptoms improved upon changing the treatment with intravenous administration of carbapenem for 14 days according to the United States CDC report [6] once the XDR *S.* Typhi was identified. He was discharged on day 23 after admission.

The emergence of *S.* Typhi strains resistant to antimicrobial agents leads to treatment failure and treatment change in antimicrobial policy. Ciprofloxacin was the drug of choice for typhoid fever in 1997 as *S.* Typhi strains were resistant to chloramphenicol, ampicillin, and trimethoprim, i.e., multidrug-resistant (MDR) since 1989 [7]. After that, the choice for treating the typhoid fever is primarily fluoroquinolones, followed by cephalosporins [4]. However, concurrent resistance to the third-generation cephalosporins by ESBL and ciprofloxacin for *Salmonella* spp. has been reported [3, 4]. Even more, XDR *S.* Typhi (accession no. LT882486.1) has been reported as an outbreak in Pakistan in 2016-2017 and as travel-associated typhoid fever [6, 8-10]. Travel-associated typhoid fever is defined as a case of typhoid fever with an onset of illness within one month after returning to the country from abroad [2, 6, 9]. Within a month of returning to Korea from a visit to Pakistan, his typhoid symptoms began and *S.* Typhi was confirmed in the blood culture.

The $bla_{CTX\text{-}M\text{-}15}$ ESBL gene and a single mutation in *gyrA* (S83F) supported the relevance between the isolate and Pakistan [4, 8-10]. In the case of suspected travel-associated typhoid fever, caution should be taken to choose empirical antimicrobial therapy. The patients with travel history to Pakistan are recommended to be treated with azithromycin for uncomplicated typhoid fever and with carbapenems for complicated typhoid fever, including encephalopathy, intestinal perforation, intestinal hemorrhage, peritonitis, hepatitis, or bacteremia [6].

In conclusion, we should pay attention to the emergence of XDR strains of *S.* Typhi because in addition to restricting the choice of antibiotics, it may be difficult to treat the typhoid fever with the existing antibiotics when these strains become the norm.

Conflicts of Interest

None declared.

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