IDCases 37 (2024) e02010

Contents lists available at ScienceDirect

IDCases

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

Case report

Cellulitis with bacteremia due to multidrug-resistant *Campylobacter jejuni* in a case of agammaglobulinemia and bronchiectasis

Itaru Nakamura [a], Takehito Kobayashi [a], Masakatsu Fukuzawa [b], Kohji Komori [c], Tetsuo Yamaguchi [c,*]

[a] *Department of Infection Prevention and Control, Tokyo Medical University Hospital, Japan*
[b] *Department of Gastroenterology and Hepatology, Tokyo Medical University Hospital, Japan*
[c] *Department of Microbiology and Infectious Diseases, Faculty of Medicine, Toho University, Japan*

A B S T R A C T

This case report demonstrates successful treatment outcomes without recurrence using fosfomycin for cellulitis with bacteremia caused by *Campylobacter jejuni* resistant to macrolides, fluoroquinolones, and tetracyclines in agammaglobulinemia and bronchiectasis. Whole-genome sequencing indicated the presence of ST137 harboring bla_{OXA-61} and *tet(O)*, with mutations in the 23S rRNA and *gyrA* genes.

Campylobacter jejuni is a leading cause of gastroenteritis, and antimicrobial resistance in C. jejuni is a growing "one health" problem, especially in livestock and other animals. Most C. jejuni infections in humans are self-limiting without any antibiotic treatment; some patients, such as immunocompromised hosts, need antibiotic treatment, mainly with macrolides, and a few develop systemic disease, such as bacteremia. In particular, invasive infection or recurrence has been detected in patients with humoral immunodeficiencies [1]. However, it remains unclear which antibiotics can be treatment option for systemic cases of drug-resistant C. jejuni infection with resistance to macrolides as main the treatment antibiotic. Fosfomycin (FOM) is a broad-spectrum antibiotic effective against both gram-positive and gram-negative organisms, including multidrug-resistant Enterobacteriaceae. Herein, we report the successful treatment of cellulitis with bacteremia caused by multidrug-resistant C. jejuni harboring resistance to macrolides, fluoroquinolones, and tetracyclines in a case of agammaglobulinemia and bronchiectasis using FOM.

Case presentation

A 47-year-old Japanese man living in Tokyo, Japan, presented with low-grade fever and left lower tibial pain, with left lower tibial redness but no diarrhea related to gastroenteritis. Due to history of agammaglobulinemia and bronchiectasis, he had been treated for multiple bacterial infections, including a case of *Helicobacter cinaedi*-induced cellulitis a few years ago. Low-dose macrolide therapy with clarithromycin (CAM) was administered for the suppression of bronchiectasis. In recent years, his antibiotic history extended to levofloxacin (LVFX), minocycline (MINO), and some β-lactams to mitigate exacerbation. He had never worked with livestock, pet breeding, or animal experimentation or traveled to developing countries. The patient's body temperature, blood pressure, and heart rate were 36.8 °C, 122/80 mmHg, and 86 bpm, respectively, at the hospital visit. Blood examination indicated an elevated white blood cell count of 9300/mm^3(normal range; 3300–8600/mm^3), a decreased platelet count of 110,000/mm^3, and an elevated C-reactive protein (CRP) level of 1.11 mg/dL but no other organ dysfunctions or impaired glucose tolerance. Oral minocycline was empirically started because of the suggested recurrence of *H. cinaedi* cellulitis. After 2 days, the patient's blood cultures turned positive, and matrix-assisted laser desorption ionization indicated the presence of *C. jejuni*. *C. jejuni* was also detected in fecal cultures despite the absence of gastroenteritis. Antimicrobial susceptibility testing by the disc diffusion method with 15 μg erythromycin (EM), 30 μg tetracycline (TC), 30 μg MINO, 5 μg LVFX, and 50 μg FOM was performed using Mueller-Hinton agar with 5 % sheep blood at 42 °C in a microaerobic environment. The results indicated resistance to EM LVFX, and TC, intermediate susceptibility to MINO, and susceptibility to FOM. After starting MINO, the cellulitis improved slowly but was not cured completely despite 10 weeks of treatment. Fecal carriage of *C. jejuni* continued at 10 weeks of minocycline treatment. Based on the results of the phenotypic antimicrobial susceptibility test and genetic analysis, antibiotic treatment was switched from minocycline to FOM, and 11

* Correspondence to: Department of Microbiology and Infectious Diseases, Faculty of Medicine, Toho University, 5–21-16, Omori-nishi, Ota-ku, Tokyo 143–8540, Japan.
E-mail address: tetsuo.yamaguchi@med.toho-u.ac.jp (T. Yamaguchi).

https://doi.org/10.1016/j.idcr.2024.e02010
Received 25 March 2024; Received in revised form 30 May 2024; Accepted 4 June 2024
Available online 7 June 2024

weeks of FOM treatment resulted in a complete clinical cure and negative fecal carriage. Two years of observation after the completion of FOM treatment showed no recurrence.

Genetic analysis

We performed draft whole-genome sequencing of the first isolated strain TUM 19981. Genomic DNA was extracted by phenol-chloroform and was subsequently purified using FastGene™ Gel/PCR Extraction Kit (Nippon Genetics Co., Ltd, Tokyo, Japan). DNA library preparation and sequencing were performed using Illumina DNA Prep (Illumina, Inc., San Diego, CA, USA) and Illumina MiSeq platform (Illumina) for paired-end reads of 300 bp using MiSeq reagent kit v3 600-cycle kit (Illumina). The Illumina reads were assembled using the CLC Genomics Workbench software ver. 20.0.4 (Qiagen). The obtained contigs were analyzed using MLST v2.0 and Resfinder v4.1 in the Center for Genomic Epidemiology website (www.genomicepidemiology.org). The genome analysis revealed that this bacterial strain was ST137, harboring bla_{OXA-61} and *tet(O),* with mutations in the 23 S rRNA gene and *gyrA* gene (Table 1). Genetic analysis showed resistance to all β-lactams, tetracyclines, macrolides, and quinolones.

Discussion

This case report presents successful treatment outcomes without recurrence using FOM to treat cellulitis with bacteremia caused by multidrug-resistant *C. jejuni* harboring resistance to macrolides, fluoroquinolones, and tetracyclines in a patient with agammaglobulinemia and bronchiectasis. It also presents the results of a genetic analysis of the drug resistance using whole-genome sequencing.

Cases of cutaneous manifestations, such as cellulitis, due to *C. jejuni* infection extremely rare in humans [2]. Additionally, drug resistance data on *C. jejuni* are limited mainly to epidemiological studies in animals and a small study in humans [3–5]. The antibiotic that should be used clinically against multidrug-resistant *C. jejuni* in immunocompromised hosts remains unclear, especially in cases of macrolide, fluoroquinolone, or tetracycline resistance. In a previous report, drug-resistant *Campylobacter coli* infection was successfully treated with amoxicillin-clavulanate (AMPC/CVA) [3]. In the present case, *C. jejuni* harbored bla_{OXA-61}, predicting resistance to AMPC/CVA. Although the strain in this case harbored *tet(O)*, conferring genetic resistance to tetracycline, phenotypic susceptibility tests revealed intermediate resistance to minocycline, a tetracycline antibiotic. Clinical improvement was partially achieved following minocycline administration, suggesting the possibility that the presence of *tet(O)* does not necessarily confer complete resistance to minocycline [5,6].

Some studies indicated in vitro activity of FOM against *Campylobacter* spp. [7,8]. The clinical efficacy of FOM for *Campylobacter* spp. is limited to old Japanese studies [9,10] and a case report. The case report presented FOM as an antibiotic treatment option for first-line drug-resistant *C. coli*-induced enteritis [11]. On the other hand, another study reported such high MICs (1.5 to > 256 mg/liter) that FOM cannot be considered active against these isolates of *Campylobacter* spp. [7]. Although FOM might become a clinical treatment option for multidrug-resistant *C. jejuni*, further clinical data are needed, and more attention to FOM drug resistance should be paid in the future.

Ethics approval and consent to participate

Written informed consent was obtained from the patient to publish this case report.

Authors' contributions

IN wrote the initial draft of the manuscript. IN and TK managed the patient's diagnosis and treatment. KK and TY performed the genetic analysis. IN, TK, MF, KK, and TY approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Table 1
Antimicrobial susceptibility testing and the whole-genome sequence.

Antimicrobial susceptibility testing		
Antimicrobial agent	**Disk diffusion method**	**Criteria**
Erythromycin	6 mm	Resistant
Tetracycline	8 mm	Resistant
Minocycline	11 mm	Intermediate
Levofloxacin	6 mm	Resistant
Fosfomycin	18 mm	-
Whole-genome sequence		
Resistance gene	**Antimicrobial agent**	**Phenotype**
Acquired		
bla_{OXA-61}	β-lactam	Resistant
tet(O)	tetracycline	Resistant
Mutation		
23 S;;23 S;;pmcs (g.2074 A>G)	macrolide	Resistant
gyrA (p.T861)	quinolone	Resistant

Consent for publication

Written informed consent was obtained from the patient to publish this case report.

Consent

We obtained written and signed consent to publish the case report.

Funding

The study received no external funding.

CRediT authorship contribution statement

Kohji Komori: Writing – review & editing, Methodology. **Tetsuo Yamaguchi:** Writing – review & editing, Supervision, Methodology. **Itaru Nakamura:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Takehito Kobayashi:** Writing – review & editing, Data curation. **Masakatsu Fukuzawa:** Data curation.

Declaration of Competing Interest

All authors declare that they have no competing interests.

Acknowledgments

We thank H. Subbaraman, PhD, from Cambridge Proofreading, LLC, for editing a draft of this manuscript.

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