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Case Report

CASE REPORT

Long-term, low-dose of clarithromycin as a cause of community-acquired *Clostridium difficile* infection in a 5-year-old boy

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Abstract

Clostridium difficile is one of the most common causes of antibiotic-associated diarrhoea. Despite *C. difficile* infection (CDI) has increased in all ages worldwide, episodes of CDI are often misdiagnosed due to the lack of clinical suspicion. Macrolides are also associated with CDI. Additionally, exposure to macrolides in the 12 weeks preceding infection is reported to be a significant risk factor of CDI in a child. We report here a 5-year-old Japanese boy who presented with acute onset of watery diarrhoea. He was diagnosed with community-acquired CDI induced by long-term (20 weeks), low-dose, oral clarithromycin for otitis media with effusion, and he recovered by conservative treatment. Physicians should be more cautious of community-acquired CDI in children who take long-term, low-dose macrolides, not to misdiagnose as diarrhoea by its side effect, and avoid unnecessary use of systemic antibiotics.

INTRODUCTION

Clostridium difficile infection (CDI) is one of the most common antibiotic-associated diseases. In the last decade, the incidence and severity of CDI as well as that of community-acquired CDI (CA-CDI) has increased globally at all ages, including children [1, 2]. Despite the increasing burden, episodes of CA-CDI are often misdiagnosed as diarrhoea by a side effect. The typical reason is the lack of clinical suspicion [3].

The most important risk factor for CA-CDI is antibiotic exposure, especially fluoro-quinolones, cephalosporin, clindamycin and ampicillin [4]. The probable risk factors for CA-CDI in children are unnecessary use of antibiotics, multiple antibiotics and a long duration of antibiotics [5]. Moreover, exposure to macrolides in the 12 weeks preceding infection is a significant risk factor of CDI in a child [6]. We report here CA-CDI in a 5-year-old boy who had long-term (20 weeks), low-dose, oral clarithromycin for otitis media with effusion (OME).

CASE PRESENTATION

A 5-year-old boy developed acute onset of watery diarrhoea and slight abdominal pain ~12 h before presentation. He experienced diarrhoea four times in half a day, and had non-worsening intermittent, abdominal pain. His medical history included prolonged OME, for which he took regular medications, including low-dose clarithromycin (5 mg/kg/day) for 20

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weeks. He did not have any prior hospitalization. There was no family history of immunosuppression or inflammatory bowel disease. He did not appear unwell, and had normal vital signs. At a physical examination, lungs were clear to auscultation and there was slight lower abdominal tenderness without peritoneal signs. Blood tests, X-rays and colon fiberscopy were not performed because his symptoms were not severe. The C. Diff Quik Chek Complete® (Alere, Tokyo, Japan) assay of stool was positive for antigen and toxin. Bacterial cultivation of stool showed CDI. Therefore, mild CA-CDI by oral clarithromycin was diagnosed.

We stopped the patient's oral clarithromycin treatment as a conservative treatment for CA-CDI because his infection was classed as mild. Furthermore, we prescribed probiotics (Bifidobacterium, 3 billion colony-forming units/day for 2 weeks) for prevention of recurrent CA-CDI. Our patient's symptoms gradually resolved after 5 days when conservative treatment was started. His symptoms disappeared after 2 weeks and remained asymptomatic without recurrence. Eight weeks after onset, he had slightly loose stools once a day for 2 days. The C. Diff Quik Chek Complete assay showed that the stool was negative for *C. difficile*. His symptoms immediately disappeared and there has been no recurrence.

Our patient had no fever, unexplained watery diarrhoea, and no other risk factors (e.g. exposure to acid-blocking medications, family members with CDI or outpatient healthcare environment), except for orally taking long-term, low-dose macrolide antibiotics [5]. At his first visit to the clinic, common viral gastroenteritis was suspected because his symptoms were acute onset and slight symptoms. However, we identified *C. difficile* glutamate dehydrogenase antigen and its toxin in the stool using the C. Diff Quik Chek Complete assay. At his first visit, both tests of the antigen and toxin were positive.

DISCUSSION

There were two important findings in our patient. First, long-term (20 weeks), low-dose clarithromycin induced CA-CDI in a child. Physicians sometimes misdiagnose CDI because macrolides can more often cause diarrhoea as a side effect. Exposure to macrolides in the 12 weeks preceding infection is reported to be a significant risk factor of CDI in a child [6]. Our report would remind physicians that long-term (20 weeks), low-dose clarithromycin induce CA-CDI. In the last decade, macrolides have continued to be prescribed, despite issues of overuse of antibiotic agents [1]. In the United States, macrolides have been increasingly prescribed in children older than 6 years for otitis media and sinusitis and in children younger than 6 years for viral infections [7]. In Japan, macrolides are more frequently prescribed with long-term administration for various diseases compared with other countries. These diseases include OME, chronic otitis media, chronic sinusitis, diffuse panbronchiolitis, chronic obstructive pulmonary disease and atypical pneumonia.

Second, unnecessary use of systemic antibiotics for OME induced CA-CDI in a child. The clinical practice guideline for OME in 2016 stated that physicians should recommend against using systemic antibiotics for treating OME [8]. Avoidance of unnecessary use of antibiotics reduces side effects, delays in definitive therapy caused by short-term improvement and then relapse, antimicrobial resistance and unwanted expenses [1].

CONCLUSION

We showed that long-term (20 weeks), low-dose oral macrolides induced CA-CDI in a child. Physicians should be more cautious of CA-CDI in children, not to misdiagnose as diarrhoea by its side effect, and avoid the unnecessary use of systemic antibiotics for OME.

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CONFLICTS OF INTEREST STATEMENT

No conflicts of interest.

ETHICAL APRROVAL

Written consent was signed by the patient's parents in order to use the medical date for scientific purposes.

GUARANTOR

Hirofumi Namiki.

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