CASE REPORT

Clarithromycin-induced haemorrhagic colitis

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SUMMARY

Haemorrhagic colitis by *Klebsiella oxytoca* has been described as an antibiotic-associated colitis, particularly with the use of ampicillin. Here we report a patient with haemorrhagic colitis caused by *K oxytoca* after the use of clarithromycin. A 67-year-old Japanese woman with diabetes presented with mucobloody diarrhoea and abdominal pain. Stool culture grew *K oxytoca*. Colonoscopy showed the appearance of haemorrhagic colitis. Further history taking revealed that she had received a course of oral clarithromycin for upper respiratory tract infection. She had recovered by conservative treatment. We should be careful about gastrointestinal symptoms in patients on clarithromycin, which can cause haemorrhagic colitis associated with *K oxytoca*.

BACKGROUND

Previous reports have shown that penicillin is the most frequent antibiotic that can cause haemorrhagic colitis associated with *Klebsiella oxytoca*; but there are some reports that indicate clarithromycin as a cause of it.¹ In addition, clarithromycin is frequently, and occasionally in a long term, prescribed by many physicians in Japan, for sinusitis, bronchitis or bronchiectasis. Our patient developed haemorrhagic colitis associated with *K oxytoca* after a course of clarithromycin, which had been prescribed for upper respiratory tract infection. Thus, we should be careful about drug-induced haemorrhagic colitis when our patients would develop diarrhoea while on clarithromycin.

CASE PRESENTATION

A 67-year-old Japanese woman with a history of diabetes mellitus presented to our hospital with a 2-day history of mucobloody diarrhoea and abdominal pain. During these 2 days, she had mucobloody diarrhoea 15 times a day and severe intermittent colicky abdominal pains over the umbilical and hypogastric regions. She denied nausea, vomiting, haematemesis, back pain, fever, chills or night sweats. The patient did not have a history of smoking, alcohol, allergy or contact with other unwell persons. Her regular medications included mitiglinide for diabetes. Her medical history included urolithiasis and retinal detachment. Her father died from cerebral haemorrhage. The patient had had a sore throat and nasal discharge for 8 days until 2 days before admission and had been prescribed clarithromycin (200 mg twice daily for 5 days) for upper respiratory tract infection.

INVESTIGATIONS

On physical examination, she was not in acute distress. Her height was 139 cm, and weight was 35 kg

(5 kg lost from the baseline). The blood pressure was 168/87 mm Hg, the heart rate 111/min, the respiratory rate 20/min, the temperature 36.6°C and the arterial oxygen saturation of 96%, while breathing ambient air. The head and neck was normal except dry tongue. There were no crackles or wheezes over the lungs. There was normal S1 and S2 but no S3, S4 nor murmur. Axillary dryness was observed. The abdominal examination showed tenderness over the umbilical region. Mucobloody stool was observed on digital rectal examination.

The laboratory tests showed the white blood cell of 11 200/ μ L, the potassium 3.5 mmol/L, the haemoglobin A1c 7.2% and the blood glucose 225 mg/dL. Other laboratory data were normal. Abdominal X-ray revealed no air-fluid level or free air. There was no abnormal finding on chest X-ray. ECG revealed sinus tachycardia with the right bundle branch block.

The stool culture grew *K oxytoca*, which can be a cause of antibiotic-induced colitis, especially haemorrhagic colitis. Clarithromycin was suspected as the culprit antibiotic. CT scan showed swelling and fluid collection of the ascending colon, which suggested right-sided colitis (figure 1). Full colonoscopy was performed and confirmed the endoscopic appearance of haemorrhagic colitis (figure 2).

Figure 1 Abdominal CT scan with contrast demonstrating oedematous ascending colon with fluid collection.

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Figure 2 Colonoscopic findings showing haemorrhagic mucosal erosions.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses in this patient included pseudomembranous colitis or *Clostridium difficile*-associated diarrhoea, infectious colitis (bacterial, toxigenic, fungal or parasitic), other types of antibiotic associated colitis (osmotic, functional or secretory) or inflammatory bowel disease (ulcerative colitis or Crohn's disease). Antibiotic-associated haemorrhagic colitis was most likely since our patient had haemorrhagic colitis after 5-day course of clarithromycin use and the stool culture grew *K oxytoca* without copathogens. Neither *Shigella spp* nor verocytotoxigenic (shiga-toxigenic) *Escherichia coli* were isolated. A CT scan showed right-sided colitis. Colonoscopic finding showed the haemorrhagic mucosal erosion without evidence of pseudomembranes. *C difficile* toxin was not identified in the stool specimen. Thus, pseudomembranous colitis and other types of antibiotic associated colitis were less likely.

Since she did not develop a relapse of this condition more than 1 year after the discharge, inflammatory bowel disease was also less likely.

TREATMENT

She was dehydrated on admission, although the modified Early Warning Score² was 3 point which did not indicate high risk. The patient received conservative treatment, including intravenous fluid for the dehydration. Adequate urine output was obtained shortly after vigorous intravenous rehydration. Although the potassium level was slightly low at first, the ECG showed QTc interval of 0.421 s which was within the normal range. After fluid replacement therapy for several days, the potassium level returned to 4.6 mmol/L. Her local primary doctor was informed that clarithromycin was the probable cause of the colitis and that the use of this antibiotic should be safely avoided in this patient.

OUTCOME AND FOLLOW-UP

The patient had recovered only by conservative treatment and she was discharged thereafter. She had been well until our last contact with her.

DISCUSSION

Our patient probably developed haemorrhagic colitis associated with macrolide antibiotic, clarithromycin. As described above, there are other forms (osmotic, functional or secretory) of antibiotic-associated colitis which were included in the differential diagnosis in this patient. Disturbance of the normal bacterial flora due to antibiotics can lead to the decreased metabolism of carbohydrates which humans cannot metabolise, thus the osmotic effect of carbohydrates can cause diarrhoea.³ It may also lead to the decreased metabolism of bile acid and excess of primary bile acid which have a secretory effect on the colonic mucosa.³ Macrolides such as erythromycin and clarithromycin are shown to have motilin-agonistic effect, which could accelerate the transit time of upper gastrointestinal tract.³ Antibiotic-associated colitis could be an effect of all macrolides, but there have been few cases with haemorrhagic colitis associated with macrolides. Thus, the clinical features in the patient were similar to those described previously as antibiotic-associated haemorrhagic colitis,^{4 5} but these were not consistent to pseudomembranous colitis, or secretory or functional diarrhoea.

Antibiotic-associated haemorrhagic colitis is known as a special form of antibiotic-associated colitis, which is usually encountered in outpatients and typically occurs after treatment with penicillin derivatives. *K oxytoca* is considered as the aetiological agent in this form of colitis.⁶ Although the toxicological properties of *K oxytoca* are still unclear and the clinical importance of infection with *K oxytoca* has been considered as somewhat variable,⁷ the probable relation between antibiotic-associated haemorrhagic colitis and *K oxytoca* strains producing cytotoxin has to be shown in the animal models.⁴

Amoxicillin has been suggested as the most frequently related agent for antibiotic-associated haemorrhagic colitis by *K oxytoca*. Quinolones and cephalosporins have been also reported as the causes of antibiotic-associated haemorrhagic colitis other than penicillin.^{8 9} This case may highlight the need to consider that clarithromycin can also be an important agent which can cause antibiotic-associated haemorrhagic colitis.

Learning points

- ▶ The use of clarithromycin can lead to antibiotic-associated haemorrhagic colitis caused by *Klebsiella oxytoca*.
- ▶ Patients with mucobloody diarrhoea while on clarithromycin should be suspected of having haemorrhagic colitis.
- ▶ Physicians should be careful about gastrointestinal symptoms in patients on clarithromycin, since this antibiotic is commonly prescribed.

Contributors RM, KK and YT cared for the patient and also have contributed significantly in writing the manuscript.

Competing interests None.

Patient consent Obtained.

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