



## Case Report

## Acute ischemic colitis with hematochezia related to baloxavir marboxil treatment for influenza A

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## ABSTRACT

Oseltamivir, an established oral anti-influenza medication, increases the risk of ischemic colitis. Baloxavir marboxil is a novel oral anti-influenza medication, and few studies have evaluated its potential side effects, including ischemic colitis. Moreover, as influenza A can also induce ischemic colitis, drug-induced colitis associated with anti-influenza medication is not clearly understood. In this report, we describe the case of a 62-year-old Japanese woman who developed acute ischemic colitis after taking baloxavir for influenza A. The day after taking baloxavir (day 2), the patient experienced abdominal pain, diarrhea, and nausea. On day 3, she had developed hematochezia and decided to visit our hospital. Upon presentation, inflammation of the descending and sigmoid colon was detected by abdominal echography and computed tomography. Fluid replacement therapy and dietary restrictions were initiated. On day 4, the inflammation of the descending colon and marked intestinal edema were confirmed by colonoscopy. She was clinically diagnosed with ischemic colitis, from which she recovered completely by day 9. This case suggests that patients taking baloxavir may be at risk of developing ischemic colitis with hematochezia and underscores the need to further study the induction of this condition by commonly used oral anti-influenza agents.

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## 1. Introduction

Baloxavir marboxil was approved by the Pharmaceuticals and Medical Devices Agency in October 2018 as a novel oral anti-influenza medication in Japan. Baloxavir's main advantage over previous anti-influenza medications, such as oseltamivir, is that it only requires a single-dose to treat influenza A. Furthermore, unlike baloxavir, oseltamivir has been reported to increase the risk of colitis, among other side effects [1]. The potential side effects of drug-induced colitis associated with anti-influenza medications are not fully understood. One study showed that recovery from colitis with hematochezia occurred in parallel with the improvement of influenza A symptoms after two weeks of zanamivir treatment [2]. As baloxavir is a new drug, few studies have evaluated its potential

side effects. In this report, we describe a case of acute ischemic colitis with hematochezia following baloxavir ingestion.

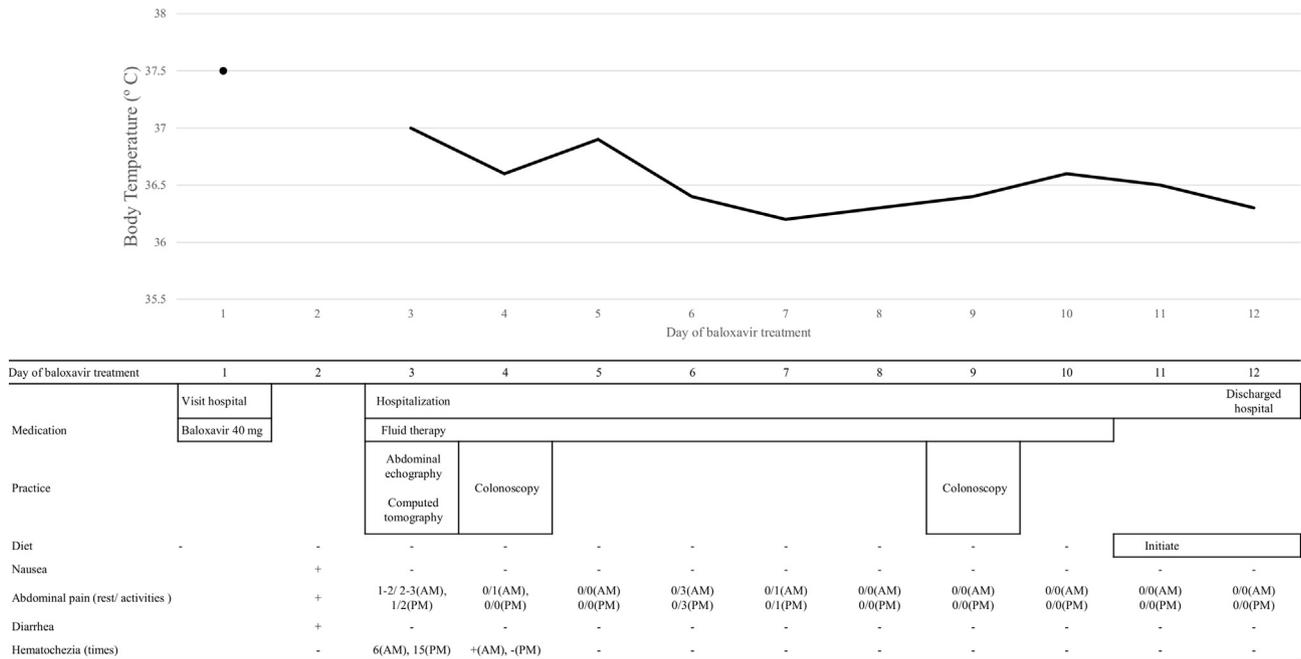
## 2. Case report

A woman aged 62 visited a clinic with a fever (37.5 °C). Her medical history included suspicion of angina pectoris and rheumatoid arthritis, and she was not taking any medications. At the clinic, she was diagnosed with influenza A by a rapid diagnosis kit (Rapid Testa Color FLU Stick; SEKISUI MEDICAL CO., LTD., Tokyo, Japan) on day 1. A single oral dose of baloxavir 40 mg, according to body weight (63.5 kg), was then administered. A single oral dose of 500 mg acetaminophen was also prescribed for fever, but not actually taken. She cannot eat foods from day 1. Patient's initial symptoms, body temperature, and prescribed medications are shown in Fig. 1.

On day 2, abdominal pain, diarrhea, and nausea occurred. On the morning of day 3, she had 7 to 8 instances of hematochezia with fever (37.5 °C), and she visited our hospital. Clinical examination upon presentation (day 3) revealed 6400/μL of white blood cells

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**Fig. 1.** Patient’s symptoms, body temperature, and medications prescribed and used for treatment of influenza A and ischemic colitis. The variations in body temperature from day 1 (the day of baloxavir administration) until the patient’s discharge (day 12) are presented. +, the patient felt nausea or developed diarrhea; -, the patient did not feel nausea or develop diarrhea. Abdominal pain is rated on the Wong-Baker Faces Pain Rating Scale as follows: 0 = No hurt, 1 = Hurts little bit, 2 = Hurts little more, 3 = Hurts even more, 4 = Hurts whole lot, 5 = Hurts worst. Numbers of hematochezia indicates the number of times abdominal pain occurred at rest/activities. AM = ante meridian, PM = post meridian.

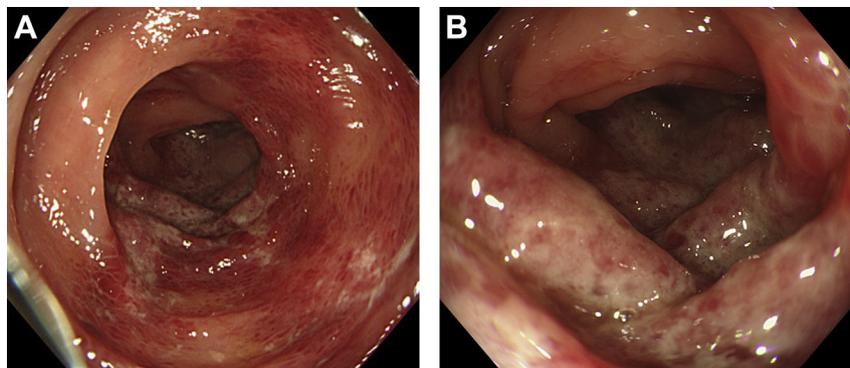
and 0.98 mg/dL of C-reactive protein. Abdominal echography showed colitis of a part of the colon. Computed tomography of the abdomen showed inflammation of the descending and sigmoid colon, and both edema and bowel wall thickening of the descending colon. She had not taken any medication except baloxavir and a drug lymphocyte stimulation test (DLST) was not performed. The microbiological culture test conducted was positive for nonpathogenic bacteria *Citrobacter farmer* and negative for *Salmonella*, *Vibrio*, *Shigella*, *Escherichia coli* O157, and *Campylobacter*. A presumptive diagnosis of acute ischemic colitis was made, and replacement fluid therapy was started with dietary restrictions. On day 4, colonoscopy results were as follows. Redness, extensive ulceration, and submucosal hemorrhage were distributed segmentally along the left side of the sigmoid colon and close to the splenic flexure. Cyanotic mucosal nodules and hemorrhagic ulcerations showed necrotic and intestinal edema. The inflamed descending

and sigmoid colon confirmed the clinical diagnosis of ischemic colitis (Fig. 2).

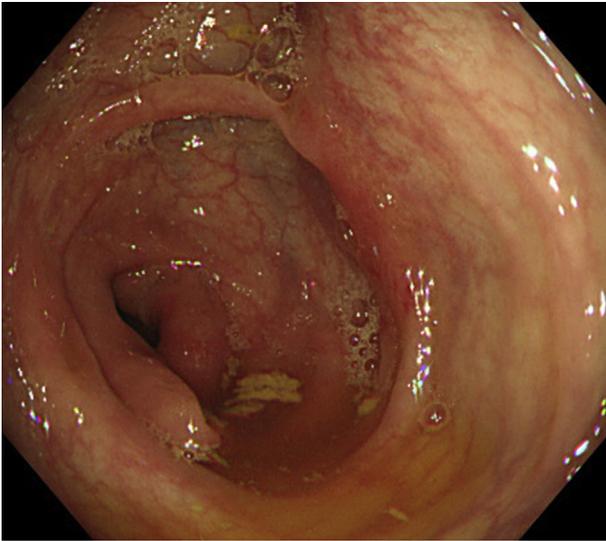
On day 7, abdominal pain, diarrhea, and nausea disappeared. On day 8, symptoms of influenza disappeared and the temperature returned to normal (36.3 °C). On day 9, recovery from ischemic colitis was confirmed by colonoscopy (Fig. 3) and an appropriate diet was initiated after two days.

### 3. Discussion

Treatment with oral anti-influenza agent oseltamivir has been associated with an increased risk of colitis with hematochezia [1,3,4], in contrast to treatment with baloxavir for which this causal relationship has been rarely reported. After ingestion of oseltamivir, patients first reported having diarrhea and abdominal pain [4]. Two days after taking oseltamivir, patients reported having other



**Fig. 2.** Colonoscopy of the patient’s descending colon on day 4 (three days after baloxavir administration). (A) Segmental distribution of redness, extensive ulceration, and submucosal hemorrhage along the left side of the sigmoid colon and close to the splenic flexure. (B) Cyanotic mucosal nodules and hemorrhagic ulcerations are consistent with necrotic and intestinal edema.



**Fig. 3.** Colonoscopy of the patient's descending colon on day 9 (eight days after baloxavir administration), showing that redness is still partly present, however, no other clinical characteristics are visible; the patient was almost completely cured.

symptoms, and they recovered 8–10 days after its discontinuation [4]. Here we report on a case of baloxavir induced-ischemic colitis, in which the first symptoms presented after ingestion (diarrhea and abdominal pain) were similar to those reported for oseltamivir, and that was also accompanied by hematochezia.

Ischemic colitis typically develops in the sigmoid and descending colon. In the present case, the site of colitis was the deep descending colon, similar to a previous report [4]. Bacterial colitis was excluded; drug-induced hemorrhagic colitis was also an unlikely diagnosis because it typically develops in the right-sided colon [5]. Furthermore, influenza A may also be a risk factor of colitis, such as ischemic and hemorrhage colitis, with hematochezia [2]. In this case, the possibility of ischemic colitis triggered by influenza cannot be completely ruled out. Our patient did not exhibit vascular risk factors, such as hypertension, diabetes, and hyperlipidemia. Therefore, in this case, the risk factor for ischemic colitis could have been an intestinal-related factor, such as increased intestinal pressure.

Here, it is possible that the risk factor of ischemic colitis was the ingestion of baloxavir because diarrhea and hematochezia only occurred after taking this medication. Baloxavir and oseltamivir can lead to ischemic colitis through the same mechanism; they both chelate metal ions [6,7]. The intake of constipation-inducing drugs is a risk factor of ischemic colitis because they reduce the blood flow and increase the intraluminal pressure [8]. Furthermore, an increase in the intestinal tract osmotic pressure may induce water movement to the intestinal tract. We speculate that baloxavir, which was excreted in feces as unchanged baloxavir and active metabolites, chelates the metal ions from food in the intestinal tract, raising osmotic pressure.

The Half-life of baloxavir and oseltamivir was 79 h and 1–3 h, respectively. Additionally, the rate of excretion in feces of baloxavir and oseltamivir was 80% and <20%, respectively [9,10]. Although, both medications have different pharmacokinetics, we found that oral baloxavir is equally capable of inducing colitis with hematochezia as oral oseltamivir [9,10].

The limitation of this case report was the fact that DLST and biopsy were not carried out. DLST is often non-specific to diagnose

hemorrhage colitis [1], while biopsies are often non-specific to diagnose ischemic colitis [11]. Therefore, the diagnosis of ischemic colitis was inferred by the patient's clinical characteristics and colonoscopy.

This case suggests that oral anti-influenza baloxavir may increase the risk of ischemic colitis with hematochezia. The risk of developing this condition associated with common oral anti-influenza agents should be further studied to better understand it and to better distinguish this condition presentation from that induced by influenza itself. This case report can guide physicians as to how to manage baloxavir treatment.

### Conflicts of interest

None.

### Authorship statement

All named authors meet the author's eligibility criteria prescribed by the International Committee of Medical Journal Editors (ICMJE) and contributed to and confirmed the contents of this manuscript.

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