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## Laninamivir-induced ischemic enterocolitis: A case report

Chihiro Suzuki, Tsuneaki Kenzaka

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### Abstract

#### BACKGROUND

Neuraminidase inhibitor-associated acute hemorrhagic colitis is rare. We report a case of ischemic enterocolitis that was likely caused by laninamivir.

#### CASE SUMMARY

A 54-year-old female patient with influenza type A was administered 40 mg of laninamivir *via* inhalation once. On the same day, the patient experienced bloody stools and lower abdominal pain. A contrast-enhanced abdominal computed tomography showed edema-like changes from the descending colon to the sigmoid colon, which suggested ischemic enterocolitis.

#### CONCLUSION

We treated a patient with ischemic enterocolitis caused by laninamivir, a rare but similar symptom following the administration of oseltamivir.

**Key Words:** Hemorrhagic colitis; Ischemic enterocolitis; Laninamivir; Influenza; Neuraminidase inhibitor; Case report

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**Core Tip:** Although a clear mechanism underlying oseltamivir-associated hemorrhagic enteritis/ischemic enterocolitis has not been elucidated, the simultaneous occurrence of the following two factors has been considered responsible for the condition: (1) Local angiospasm and vasculitis due to the effect of an allergic reaction to oseltamivir; and (2) Hypoperfusion in the intestinal tract due to the effect of dehydration caused by influenza. Laninamivir is considered to demonstrate the same mechanism as oseltamivir.

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## INTRODUCTION

Influenza is an infectious disease with a repetitive winter cycle. According to a report from the National Institute of Infectious Diseases, Japan, of a total population of 126 million in the country, an estimated 12 million individuals (population ratio, 9.5%) were affected by influenza during the 2018–2019 season, and 7.28 million individuals were affected during the 2019–2020 season (population ratio: 5.7%)[1]. In 2018, 3325 deaths were reportedly due to influenza[1]. In a meta-analysis of placebo-controlled clinical studies of oseltamivir in all adults, the oseltamivir group was observed to have a shortened duration of seasonal influenza and a reduced risk of hospitalization[2]. Additionally, a decrease in the influenza-associated mortality rate has been reported with the administration of neuraminidase inhibitors as the first-line of treatment[3].

Neuraminidase inhibitors approved in Japan include oral oseltamivir, inhaled zanamivir and laninamivir, and intravenous peramivir. Adverse reactions to neuraminidase inhibitors are usually mild; however, they can cause bronchospasm in patients with asthma or chronic obstructive pulmonary disease[4] and other relatively common adverse reactions such as nausea/vomiting and diarrhea. Similarly, rare occurrences of acute hemorrhagic colitis (hemorrhagic enterocolitis/ischemic enterocolitis) associated with neuraminidase inhibitors have been reported[5].

Here, we report the case of a patient with ischemic enterocolitis that was considered to have been caused by laninamivir.

## CASE PRESENTATION

### Chief complaints

Lower abdominal pain and bloody stools.

### History of present illness

During winter, a 54-year-old female patient with no significant medical history presented with general malaise and a fever of 39.2°C. The next day (the second day of symptom onset), the patient visited a nearby medical institution.

Her blood pressure was 115/60 mmHg, and her pulse rate was regular with 77 beats/min.

At the same institution, the patient was diagnosed with influenza type A using a rapid antigen kit (Quick Navi-Flu2 Influenza Diagnostic Kit, Otsuka Pharmaceutical Co., Ltd. Tokushima, Japan), and she was administered a dose of 40 mg laninamivir *via* inhalation. Approximately three hours after inhalation on the same day, the patient reportedly experienced bloody stools and lower abdominal pain while sleeping at night. On the third day of symptom onset, the patient visited our institution and was hospitalized due to persistent intermittent lower abdominal pain every 20 min and bloody stools at a frequency of ten times a day. No oral medication, including any anti-platelets/anticoagulants, was prescribed.

### History of past illness

Nothing in particular.

### Personal and family history

Nothing in particular.

### Physical examination

Upon clinical examination, the patient appeared lucid. Her blood pressure was 125/67 mmHg, pulse rate was regular with 67 beats/min, body temperature was 36.7°C, respiratory rate was 16 breaths/min, and SpO<sub>2</sub> was 97% at room air. No pallor was observed on the palpebral conjunctiva. Heart sounds were regular, and there were no cardiac murmurs. Breath sounds were clear. The abdomen was flat and soft, with tenderness on the left flank. There was no rebound tenderness or muscle guarding. Bowel peristaltic sounds did not increase or decrease, and no palpable mass or hemorrhage was observed on rectal examination. There was no edema in the extremities, and no signs of cyanosis were observed. Her mouth was dry, and the capillary refilling time was four seconds, which suggested dehydration.

### Laboratory examinations

Blood test results revealed the following: white blood cell count, 7810/ $\mu$ L; hemoglobin, 12.9 g/dL; platelet count,  $20.7 \times 10^4$ / $\mu$ L; L-dimer, 1.0  $\mu$ g/mL; blood urea nitrogen, 17.7 mg/dL; creatinine, 0.47 mg/dL; creatinine kinase, 75 U/L; aspartate aminotransferase, 17 U/L; alanine aminotransferase, 13 U/L; lactate dehydrogenase, 155 U/L; alkaline phosphatase, 210 U/L; C-reactive protein, 3.08 mg/dL; and glycated hemoglobin A1c, 5.9%. She had no abnormalities, such as diabetes mellitus or liver dysfunction, which could manifest in ischemic episodes. Stool culture tests were performed for normal intestinal flora alone, and *Salmonella* growth was not observed. Polymerase chain reaction was not performed to detect bacteria in stools, and the stool was negative for *Clostridium difficile* toxin A and B.

### Imaging examinations

Abdominal contrast-enhanced computed tomography showed edema-like changes that extended from the descending colon to the sigmoid colon (Figure 1).

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## FINAL DIAGNOSIS

Based on the patient's clinical symptoms and imaging, her condition was diagnosed as ischemic enterocolitis.

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## TREATMENT

Fluid replacement was administered for bowel rest, and food and drink intake was withheld. For influenza type A, laninamivir had been administered *via* inhalation two days ago, and the patient was kept in a private room and followed up with symptomatic treatment. On the second day of hospitalization, fresh blood in the stool disappeared, and abdominal pain improved. On the third day of hospitalization, the patient started eating again, which did not worsen the symptoms. The patient was discharged on the fifth day of hospitalization.

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## OUTCOME AND FOLLOW-UP

Lower gastrointestinal endoscopy performed following hospital discharge (8 d after admission) showed a longitudinal ulcer extending from the descending colon to the sigmoid colon and circumferential edema-like changes (Figure 2). Histopathological examination of the same region (Figure 3) revealed stromal edema, hemorrhage, and inflammatory cell infiltration, with a prominent tendency for detachment of the superficial epithelium. These findings were consistent with those observed in ischemic enterocolitis. She had a score of seven points on the Naranjo algorithm for the adverse drug reaction causality assessment scale[6]. Therefore, the patient was diagnosed with laninamivir-induced ischemic enterocolitis. No recurrence of ischemic enterocolitis has been observed in the last five years since the patient presented to us.

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## DISCUSSION

We present a case of ischemic enterocolitis that was considered to be caused by laninamivir. Although there have been a few reports of acute hemorrhagic colitis caused by neuraminidase inhibitors, to the best of our knowledge, this is the first reported case of acute hemorrhagic colitis caused by laninamivir.

In total, 13 reports of acute hemorrhagic colitis associated with neuraminidase inhibitors, which were published between 2005 and 2020, are shown in Table 1[5,7-14]. All previous cases have been attributed to oseltamivir. The age of onset ranged from 12 to 61 years, and there have been no reports of onset among the elderly. Among the 13 patients, nine were female individuals. The time of onset was four

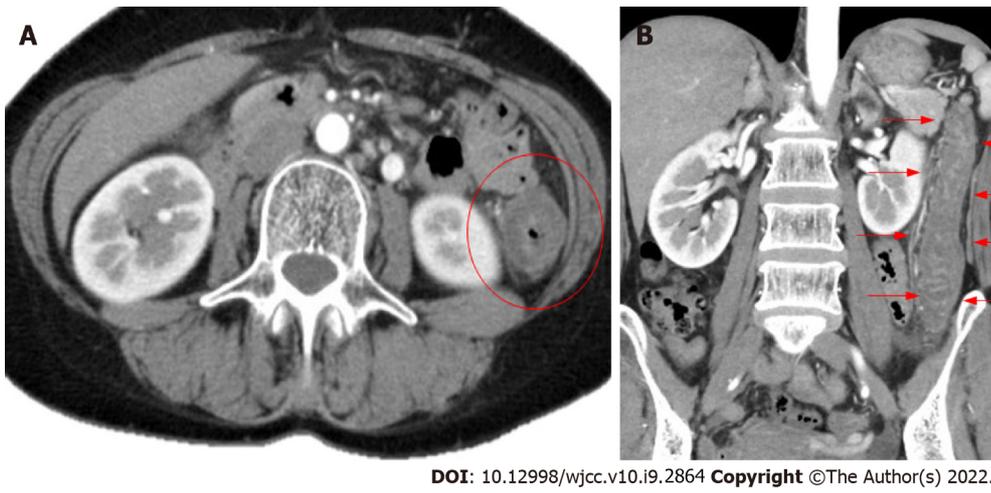
Table 1 Summary of reports of acute hemorrhagic colitis associated with neuraminidase inhibitors

Patient	Ref.	Publication year	Age (yr)	Sex	Influenza type	Medication used	Time from use of medication to onset	Symptoms	Endoscopic findings
1	[5]	2005	58	Female	A	Oseltamivir	2 d	Diarrhea, abdominal pain, and bloody stools	Longitudinal ulcer from the descending colon to the left side of the transverse colon
2	[7]	2006	28	Female	B	Oseltamivir	2 d	Bloody stools	Erosion, edema, and hemorrhage on the left side of the transverse colon
3	[8]	2007	20	Female	Unknown	Oseltamivir	2 d	Melena and abdominal pain	Erosion, redness, and edema in the descending colon
4	[8]	2007	50	Female	Unknown	Oseltamivir	2 d	Diarrhea, bloody stools, abdominal pain	Erosion and suspicion of ischemic enterocolitis on the left side of the colon
5	[8]	2007	30	Male	Unknown	Oseltamivir	2 d	Abdominal pain, diarrhea, and melena	Edema-like necrotic material and suspicion of ischemic enterocolitis from the sigmoid to the descending colon
6	[8]	2007	28	Female	Unknown	Oseltamivir	2 d	Abdominal pain and bloody stools	Hemorrhage, erosion, edema, and redness on the left side of the transverse colon
7	[8]	2007	50	Female	A	Oseltamivir	2 d	Bloody stools	Redness and ulceration in the descending colon
8	[9]	2013	32	Female	A	Oseltamivir	2 d	Bloody stools and tenesmus	Redness, ulcer, and mucosal edema in the rectum
9	[10]	2007	61	Male	A	Oseltamivir	1 d	Abdominal pain, diarrhea, and bloody stools	Mucosal edema, hemorrhage, and longitudinal ulcer in the entire colon
10	[11]	2011	40	Female	A	Oseltamivir	4 h	Abdominal pain, diarrhea, and bloody stools	Redness, edema, erosion, and hemorrhage in the descending colon
11	[12]	2015	31	Female	A	Oseltamivir	2 d	Abdominal pain and bloody diarrhea	Not performed
12	[13]	2016	12	Male	Unknown	Oseltamivir	4 d	Bloody stools	Not performed
13	[14]	2020	14	Male	A	Oseltamivir	Immediately after (time not specified)	Abdominal pain, nausea, and bloody stools	Findings of ischemic enterocolitis (details not specified)

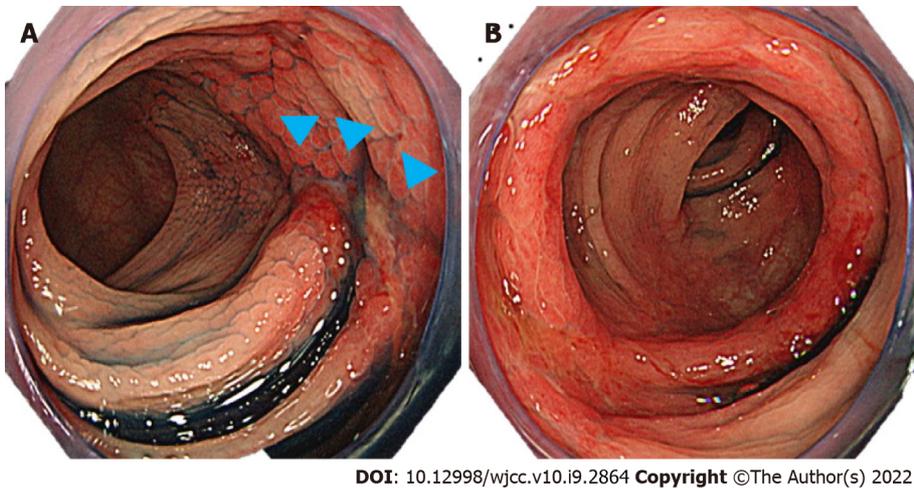
days following oral administration of oseltamivir in one patient; however, in the remaining patients, acute onset was observed immediately-to-within two days following the oral administration of oseltamivir. The descending colon was the most common site of onset. The outcome was favorable after discontinuation of the drug and conservative treatment; however, in patient 13, the hemoglobin level decreased to 3.8 mg/dL, which necessitated red blood cell transfusions.

Our patient was a middle-aged female individual without any risk factors; however, she developed ischemic enterocolitis within half a day after the administration of laninamivir *via* inhalation. Consistent with the previously reported patient who experienced hemorrhagic enteritis/ischemic enterocolitis after the oral administration of oseltamivir[5,7], this patient was diagnosed with ischemic enterocolitis induced by laninamivir, which is a neuraminidase inhibitor similar to oseltamivir.

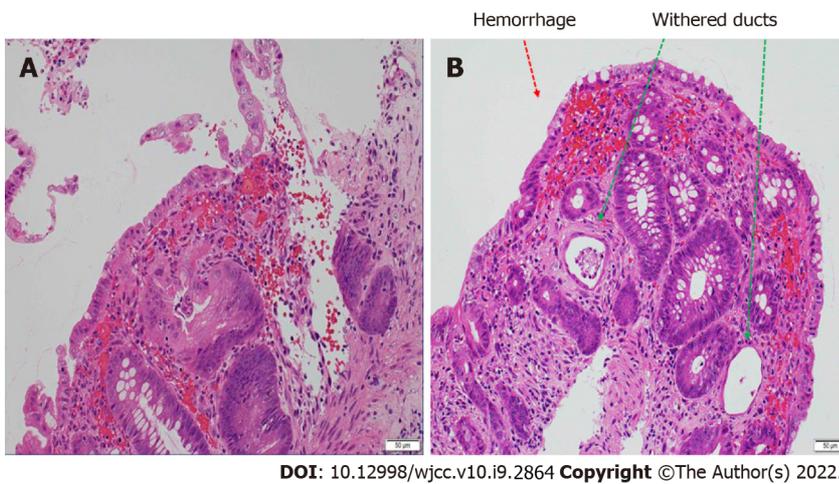
Although a clear mechanism underlying oseltamivir-associated hemorrhagic enteritis/ischemic enterocolitis has not been elucidated, simultaneous occurrence of the following two factors has been considered responsible for the condition: (1) Local angiospasm and vasculitis due to the effect of an allergic reaction to oseltamivir; and (2) Hypoperfusion in the intestinal tract due to the effect of dehydration caused by influenza[9,12]. Laninamivir is considered to demonstrate the same mechanism as oseltamivir. Approximately three hours after inhalation, she reportedly experienced bloody stools and lower abdominal pain. In addition, she developed certain symptoms shortly after inhalation and a possible allergic reaction. Similarly, she was dehydrated based on physical findings. Therefore, the mechanism underlying oseltamivir-associated ischemic enterocolitis in this patient is considered related to these factors.



**Figure 1 Contrast-enhanced abdominal computed tomography.** A: Horizontal slice; B: Coronal slice edema-like changes are observed from the descending colon to the sigmoid colon (red circle, red arrow).



**Figure 2 Lower gastrointestinal endoscopy.** A: Longitudinal ulcer (sagittal head); B: Edema-like changes are observed.



**Figure 3 Histopathological examination of lesions in the colon (hematoxylin-eosin staining).** A: Stromal edema and hemorrhage, infiltration of inflammatory cells, and a tendency for detachment of superficial epithelial are observed; B: Withered ducts (green arrow) and hemorrhage (red arrow) are observed.

During treatment for influenza, attention should be paid not only to respiratory tract symptoms such as pyrexia, cough, and sputum but also to abdominal symptoms.

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## CONCLUSION

In conclusion, we treated a patient with ischemic enterocolitis that was considered to be caused by laninamivir. The onset of ischemic enterocolitis, although rare, has been reported following the administration of oseltamivir. Similarly, laninamivir may cause similar abdominal symptoms through the same mechanism; thus, caution should be exercised during the administration of this medication.

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## FOOTNOTES

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