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Abstract

Collagenous colitis (CC) is one of the causes of undefined watery diarrhea, which is histologically accompanied by a thickening of the subepithelial collagen layer. CC associated with lansoprazole normally occurs within several weeks after the initial administration, but no case presenting after the long term administration of lansoprazole has yet been reported. A 77-year-old male with a history of 6-year administration of lansoprazole complained of watery diarrhea and weight loss. A colonoscopy revealed the disappearance of vascular networks and red spots in the sigmoid colon. The biopsy specimen showed erosion and collagen bands thickened, so the patient was diagnosed as CC. After lansoprazole discontinuation, the watery diarrhea disappeared and histological abnormalities improved.

Introduction

Collagenous colitis (CC) which is a type of the microscopic colitis was first reported by Lindstrom (1) as a disease causing chronic watery diarrhea. CC has mostly been reported from European or North American centers, but the disease occur worldwide (2-4). A thickening of the subepithelial collagen layer is histologically observed together with a chronic mononuclear inflammation in the lamina propria (5) while the morphological features of CC revealed upon endoscopy and radiological examination have not yet been clarified. The cause of microscopic colitis remains for the most part unclear, but it is probably due to specific mucosal responses in individuals predisposed to various noxious luminal agents. The concept that some drugs may cause or worsen microscopic colitis was proposed in the early 1990s (6). The first well-documented case of drug-induced CC was published in 1994 (7). Lansoprazole is one of the drugs which may cause CC within several months of the administration periods (8). We herein reported a case of CC after a 6-year administration of lansoprazole.

Case report

A seventy-seven year-old male with a history of prostatectomy for prostate cancer and the 6-year administration of lansoprazole for the treatment of gastro-esophageal reflux disease was admitted to our hospital complaining of watery diarrhea with five to

ten bowel movements a day for two months and 4 kg weight loss. The patient had taken clarithromycin for two weeks to treat his bronchitis and after three months the watery diarrhea began. A physical examination and a routine blood test showed no abnormal findings. Clostridium difficile toxin and other pathogenic bacteria were not detected in a stool culture. The first colonoscopy performed after admission to our hospital revealed the disappearance of vascular networks and numerous red spots in the sigmoid colon and descending colon (**Figure 1A**). All biopsy specimens obtained from the lesions of descending and sigmoid colon showed erosion with severe infiltration of inflammatory cells (**Figure 1B**). Masson's trichrome staining identified subepithelial collagen bands as thick as 25 μm in every specimen (**Figure 1C**). The patient was diagnosed to have CC based on these histological findings. A CT examination detected neither ascites nor intestinal abnormality. As lansoprazole has been reported to be a causative drug for CC, its administration was therefore suspended. Within a few days of suspending administration, the watery diarrhea disappeared. The second colonoscopy was performed two months after suspended lansoprazole and a reduction in the number of red spots was thus observed (**Figure 2A**). The biopsy specimens obtained from the cecum, ascending colon, transverse colon, descending colon and rectum showed no collagen bands. Only the specimens obtained from the sigmoid colon revealed

diminished collagen bands on hematoxylin-eosin staining (**Figure 2B**) and faint bands as thin as 9 μm on Masson's trichrome staining (**Figure 2C**).

Discussion

The present study detailed a case of CC which occurred after the long-term, 6-year administration of lansoprazole and restored the symptoms, endoscopic and histological findings related to CC by suspending lansoprazole. Whereas the durations from the beginning of lansoprazole administration to the appearance of CC were reported from a few days to 10 months (8-14) (**Table**), our case showed a much longer duration of lansoprazole administration before presenting the CC-related symptoms. This suggests that a long-term follow-up for CC is required for the patients that are administered lansoprazole.

While the pathogenesis of CC has not yet been clarified, some drugs including non-steroidal anti-inflammatory drugs (NSAIDs) (6), ticlopidine (15), cimetidine (16) as well as lansoprazole (8-14) are thought to cause CC. The possible mechanisms for the induction of CC by lansoprazole is that the proton pump of the intestinal epithelia is inhibited by lansoprazole, leading to an abnormality in the microflora, an altered absorption of the bile juice and a change in pH (17), the reaction of the immune system

and direct toxic effects on the intestinal epithelia by lansoprazole or its metabolite within a year (9). In contrast, the pathogenesis of CC after such a long-term administration of lansoprazole, as observed in our case, remains unknown, however, it is clear that the discontinuation of lansoprazole alone improved the CC symptoms without any other treatments. The patient had taken clarithromycin for two weeks and after three months the diarrhea began. Clarithromycin is known to be an inhibitor of cytochrome P450 (CYP) 3A4 which plays a role in the metabolism of lansoprazole (18). It is reported that the inhibition of CYP3A4 is slowly reversible, resulting in the prolonged reduction of CYP3A4 activity (19). Therefore, it is speculated that the plasma lansoprazole concentration increased by the inhibition of CYP3A4, and may develop a collagenous colitis in this case. A further analysis with a large number of CC patients is warranted to elucidate the mechanism for the development of CC induced by the long-term administration of lansoprazole. Although most cases of CC were thought to show no characteristic findings on endoscopy (20), it is noteworthy that lansoprazole-induced CC frequently showed colonic ulceration including longitudinal ulcer (14). Cruz-Correa, et al. suggested that the longitudinal ulcer in CC was due to the extension by infused air during an endoscopic examination (21). In our case, colonoscopy detected the slight changes as a disappearance in the vascular networks and

numerous red spots which were not specific for CC.

In summary, we herein described a CC case caused by the long-term, 6-year administration of lansoprazole and which recovered after suspending the lansoprazole administration. Colonoscopy revealed the disappearance of vascular networks and numerous red spots but could not detect any specific findings for CC.

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Figure Legends

Figure 1 The first colonoscopy showed the disappearance of the vascular networks and numerous red spots in the sigmoid colon (**A**). The biopsy specimen showed erosion with severe infiltration of the inflammatory cells (**B**). Masson's trichrome staining identified collagen bands that were as thick as 25 μm (**C**).

Figure 2 The second colonoscopy after suspended lansoprazole revealed a reduction in the number of red spots (A). The biopsy specimen showed a mild infiltration of the inflammatory cells with no erosion (B). The thickened collagen bands were unclear with Masson's trichrome staining (C).

Table Clinical and pathological findings of lansoprazole-associated collagenous colitis

Author	Age	Sex	Duration of LPZ administration	Duration until diagnosis	Endoscopic appearance	Collagen band	Symptom	Treatment
1. Wicox 2002 ⁸⁾	51	F	A few days	4 months	Normal	NA	Water diarrhea	Discontinuance of LPZ
2. Thomson 2002 ⁹⁾	51	M	1 week	NA	Normal	NA	Water diarrhea	Discontinuance
3. Rammer 2005 ¹⁰⁾	57	M	4 weeks	4 weeks	Normal	10µm	Water diarrhea	Loperamide
4, 5. Hilmer 2006 ¹¹⁾	53	F	7 months	2 months	Normal	NA	Water diarrhea	Discontinuance of LPZ Loperamide, Budesonide Cholestyramine, Codeine
	79		2 weeks	NA			Abdominal pain	
6. Wickbom 2006 ¹²⁾	80	F	NA	3 weeks	Mucosal tears	40µm	Diarrhea	NA
7, 8. Chande 2007 ¹³⁾	78	F	6 weeks	12 weeks	Normal	NA	Water diarrhea	Replaced with RPZ
	65		2 weeks	5 months			Weight loss	
9-17. Umeno 2008 ¹⁴⁾	71.4	M 2	3 weeks –	2 weeks –	Linear mucosal defect (7)	45µm (12.5–50µm)	Water diarrhea (9)	Discontinuance of LPZ
	(37-92)	F 7	10 months	8 months			Hematochezia (2)	
18. Our case	78	M	6 years	4 months	Indistinct vascular transparency	25µm	Water diarrhea Weight loss	Discontinuance of LPZ

F: female, M: male, LPZ: lansoprazole, NA: not available, RPZ: rabeprazole











