

[ CASE REPORT ]

## Esophageal Ulcers Associated with Ulcerative Colitis: A Case Series and Literature Review

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### Abstract:

Ulcerative colitis, a chronic and recurrent inflammatory disease, is localized to the colonic mucosa but can affect other organs and lead to various complications. Gastroduodenitis associated with ulcerative colitis has been reported. However, little is known about esophageal ulcers. We herein report two rare cases of esophageal ulcers associated with ulcerative colitis. Furthermore, the clinical and histological characteristics of 18 previously reported cases are summarized. This case series and literature review will encourage the accurate diagnosis and treatment of esophageal ulcers associated with ulcerative colitis.

**Key words:** ulcerative colitis, esophageal ulcer, manifestation

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### Introduction

Ulcerative colitis (UC) is primarily a disease of the colon; however, extracolonic manifestations have been described. Extracolonic manifestations particularly involve the blood, joints, skin, biliary tracts, liver, kidneys, lungs, and upper digestive tract (1). Gastroduodenitis associated with UC (GDUC) has been noted in 7.6% of severe cases of UC (2, 3), making it a common extracolonic manifestation of UC. In contrast, there have been relatively few reports of esophageal ulcer occurring as an extracolonic manifestation of UC (4).

We herein report two cases of UC complicated with esophageal ulcers. Furthermore, we review 18 previously reported cases of esophageal ulcers associated with UC. We summarize these cases to help characterize esophageal ulcer occurring as a complication of UC.

### Case Reports

#### Case 1

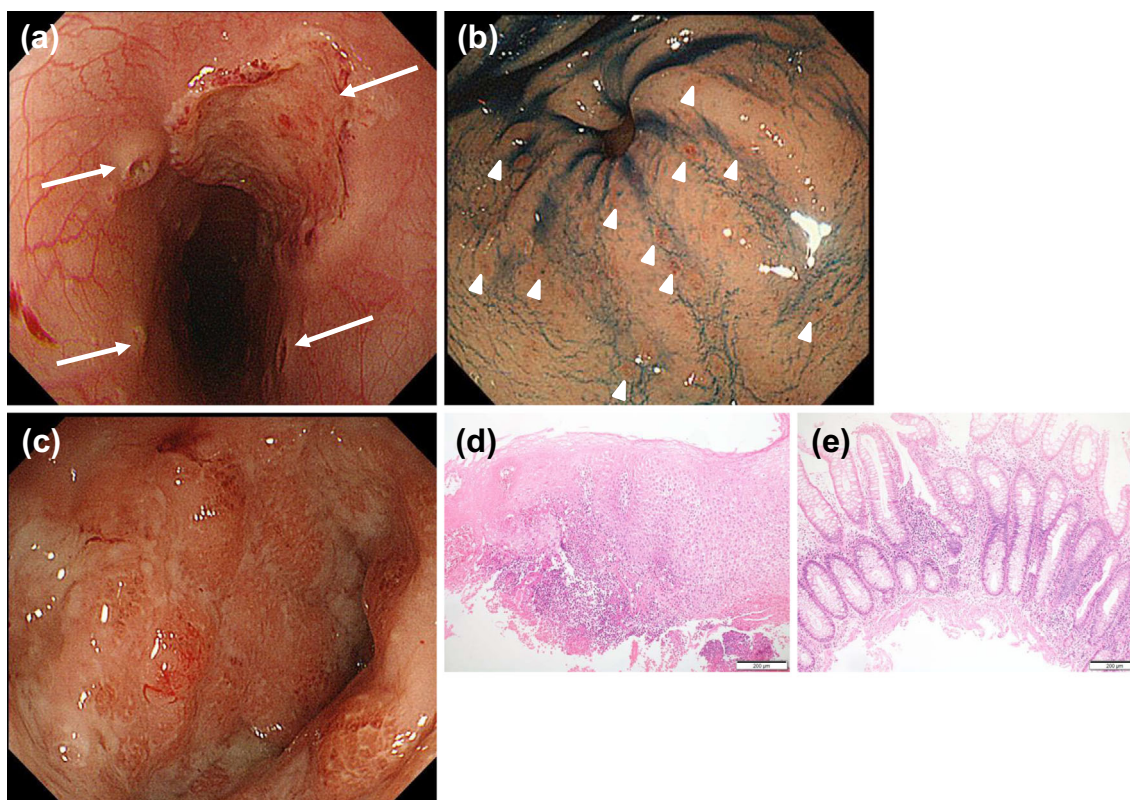
A 16-year-old girl presented with chest pain and diarrhea with blood and mucus. No oral, genital ulcers or skin lesions were evident. Esophagogastroduodenoscopy (EGD), showed an ulcer with aphthae in the esophagus (Fig. 1a) and diffuse aphthae in the stomach (Fig. 1b). A histological examination of the esophageal ulcers showed severe inflammatory cell infiltration (Fig. 1d), and the gastric erosions revealed focally enhanced gastritis. Colonoscopy revealed superficial ulcers and mucosal friability (Fig. 1c) from the rectum to the cecum. The terminal ileum was normal. In the histological examination, inflammatory cell infiltration with cryptitis was detected in the sigmoid colon and rectum (Fig. 1e); therefore, pancolitis-type UC was diagnosed comprehensively.

She was not taking any medicine, including non-steroidal anti-inflammatory drugs, and *Helicobacter pylori* infection was not confirmed. A serological examination of viral infec-

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**Figure 1.** Esophagogastroduodenoscopy (EGD), colonoscopy, and their pathological findings. (a) EGD showing an ulcer with aphthae (arrows) in the mid intrathoracic esophagus. (b) EGD showing widespread aphthae (arrowheads) at the antrum. (c) Colonoscopy showing erythema and mucosal friability in the sigmoid colon. (d) Biopsy specimen from the esophageal ulcers showing severe inflammatory cell infiltration [Hematoxylin and Eosin (H&E) staining,  $\times 100$ ]. (e) Biopsy specimen from the colon showing inflammatory cell infiltration with cryptitis in the rectum (H&E staining,  $\times 100$ ).

tions (varicella zoster virus, herpes simplex virus, cytomegalovirus, and Epstein-Barr virus-DNA) was also negative. Therefore, esophageal ulcers and gastroduodenitis associated with UC (GDUC) were diagnosed.

Treatment with intravenous prednisolone (60 mg/day) was started, and her chest pain and diarrhea were resolved in a few days. EGD on the seventh day showed healing of the esophageal ulcers (Fig. 2a) and gastroduodenal aphthae (Fig. 2b). Colonoscopy showed improvement in the inflammation of the colon (Fig. 2c). She has experienced no relapse for two years.

### Case 2

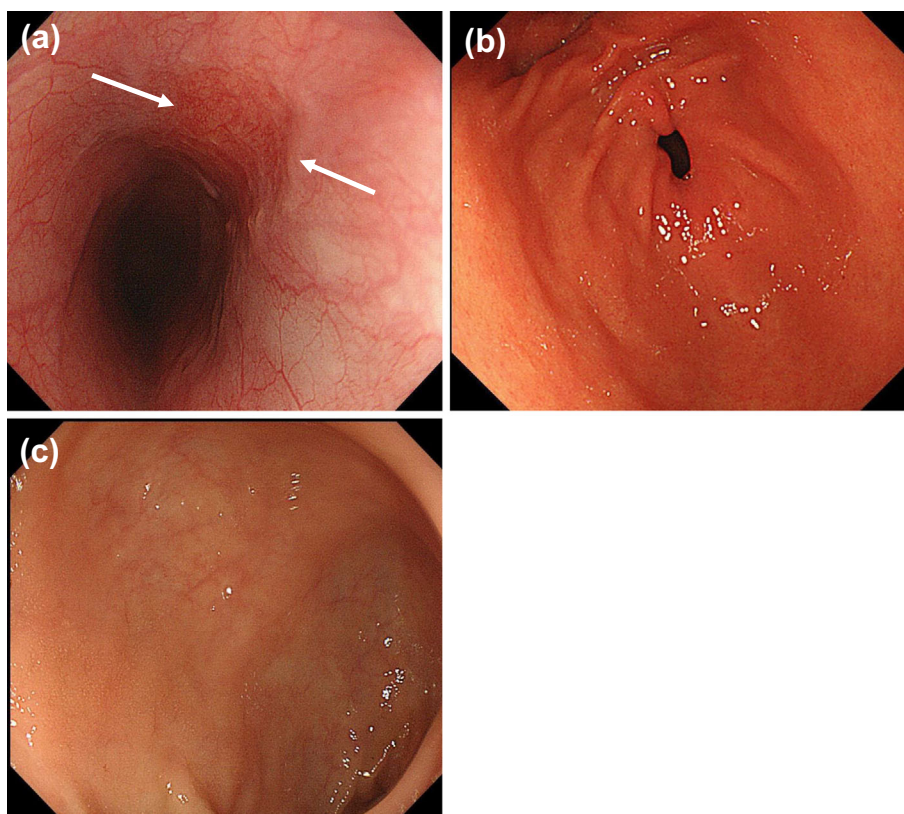
A 19-year-old woman was admitted to our hospital due to bloody stool and chest pain on swallowing. She was not taking any medication. Laboratory tests showed hypoalbuminemia, mild anemia and inflammatory responses: total protein (6.9 g/dL), albumin (2.8 g/dL), hemoglobin (10.1 g/dL), white blood cell ( $4,140/\text{mm}^3$ ), mild neutrophilic leukocytosis (61.6%), thrombocytosis (platelets  $28.9 \times 10^4/\mu\text{L}$ ), and increased C-reactive protein levels (6.88 mg/dL). Stool cultures were normal. Serological assays for viruses, including herpes simplex, cytomegalovirus, varicella, and Epstein-Bar did not demonstrate primary infection. Because of her

mouth and chest pain symptoms, EGD was performed, showing a longitudinal ulcer in the lower esophagus (Fig. 3a) and oral ulcers. Histologic findings showed infiltration of inflammatory cells in the epithelia (Fig. 3d). Colonoscopy showed superficial ulcers and mucosal friability (Fig. 3b) in the entire colon, from the rectum to the cecum. We also detected mucosal friability in the terminal ileum (Fig. 3c). The histologic findings here showed inflammatory cell infiltration with basal plasmacytosis in the transverse colon and inflammatory cell infiltration with cryptitis in the rectum (Fig. 3e). She was diagnosed with esophageal ulcer complicated with pancolitis-type UC comprehensively.

Induction therapy was started with intravenous prednisolone (50 mg/day). Thereafter, her bloody stool and pain on swallowing improved within one week. EGD after four weeks showed healing of the oral and esophageal ulcers (Fig. 4a). Colonoscopy after four weeks also showed complete remission (Fig. 4b). She has shown no relapse of esophageal lesions for one year.

### Discussion

In 1961, Margoles et al. (5) first reported a case of pancolitis-type UC with esophagitis. There have been 18 re-



**Figure 2.** Esophagogastroduodenoscopy (EGD) and colonoscopic findings. (a) EGD showing marked healing of the esophageal ulcers (arrows). (b) EGD showing healing of the gastroduodenal aphthae. (c) Colonoscopy showing improvement of mucosal edema and vascular appearance of the sigmoid colon.

ported cases of esophageal ulcers associated with UC, and we encountered 2 new cases ourselves. The previously reported cases of esophageal ulcers associated with UC (case 3 to 20) and our new cases (case 1 and 2) are summarized in Tables 1-3.

We reviewed these 20 cases and summarized their findings in Table 1 (4-16). The average age of the patients was 28.2 years (range 14-53), and the ratio of men to women was 14:6. The duration of UC was from 0 to 21 years. There were 13 cases of pancolitis, 3 cases of left-side colitis, 1 case of right-side colitis, and 3 cases with unknown details. Seven of the 18 cases had esophageal ulcers at the onset of UC, and 2 cases had ulcers at the time of UC relapse. Two cases were in UC remission, and 7 cases occurred after total colectomy. According to the review results, esophageal ulcer complications were relatively common in the young compared with the elderly. Furthermore, esophageal ulcer was often complicated in patients at the onset of colitis, or at the time of relapse. It has been reported more aggressive UC entities, such as active pancolitis, may be related to the development of gastroduodenitis associated with UC (GDUC) (2). Furthermore, cases of esophageal ulcers after surgery indicate UC may not be resolved in other organs, even after total colectomy (3).

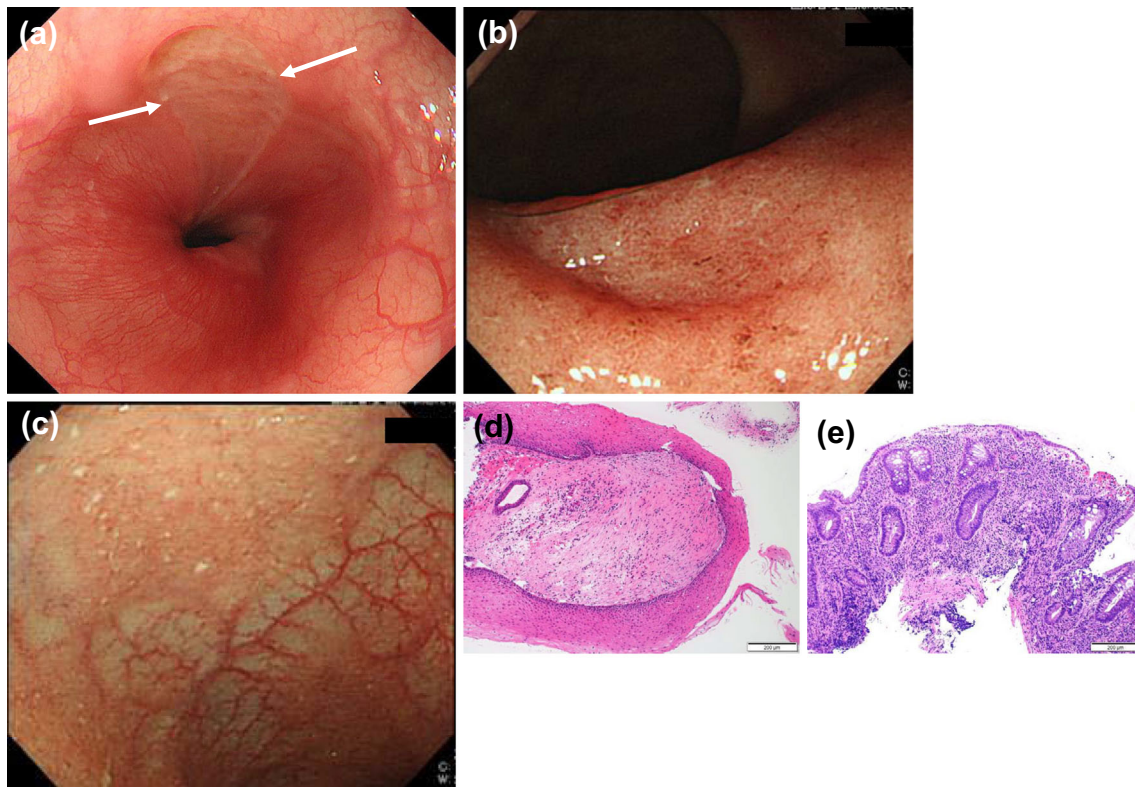
Of the 20 cases, there were 4 cases of multiple esophageal ulcers. There were two cases of entire esophageal ulcer,

five of mid-esophageal ulcer, two of lower to middle esophageal ulcer, and five with unknown details. Endoscopic findings of esophageal ulcer complicated with UC were different from GDUC. While GDUC was defined as friable and granular mucosa (2, 3), esophageal ulcer complicated with UC is a punched-out ulcer and mostly occurs in the middle to the lower esophagus.

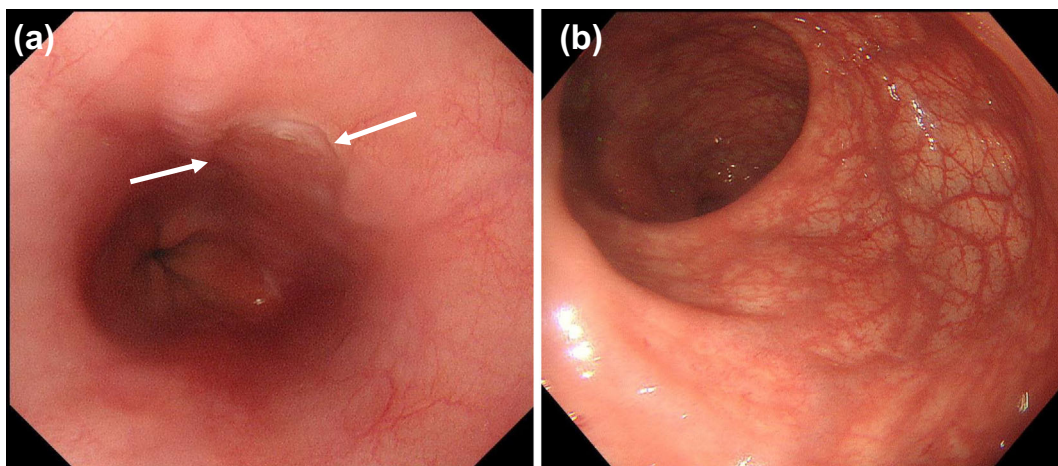
Regarding the pathology, in all cases described, only non-specific inflammatory cell infiltration was observed, with no UC-specific findings reported. Although the relationship between the esophageal ulcers and UC was not confirmed histologically, no other causes of esophageal ulcers were identified, and treatment for UC was also effective for the esophageal lesions. Regarding treatment, 10 cases were treated with prednisolone, and 2 cases received 5-aminosalicylate. GDUC is treated with medications similar to those used for UC (3, 17) and is more responsive to treatment, showing less frequent relapse than colitis. Our two newly reported cases followed a similar course.

Of the 18 reported cases, 45% had other complications, namely oral lesions in 7 cases, skin lesions in 6 cases, arthritis in 3 cases, and pancreatitis in 1 case. The case reported by Knudsen and Sparberg (6) had a generalized maculopapular eruption as a complication associated with pancolitis-type UC. The patient reported by Rosendorff (7) had buccal ulceration and arthritis. Most cases of UC with





**Figure 3.** Esophagogastroduodenoscopy (EGD), colonoscopy, and their pathological findings. (a) EGD showing a longitudinal ulcer in the lower esophagus. (b) Colonoscopy showing mucosal friability in the rectum. (c) Colonoscopy showing mucosal friability in the terminal ileum. (d) Biopsy specimen from the esophageal ulcers showing infiltration of inflammatory cells in the epithelia [Hematoxylin and Eosin (H&E) staining,  $\times 100$ ]. (e) Biopsy specimen from the rectum showing inflammatory cell infiltration with basal plasmacytosis and cryptitis (H&E staining,  $\times 100$ ).



**Figure 4.** Esophagogastroduodenoscopy (EGD) and colonoscopic findings. (a) EGD showing healing of the esophageal ulcers. (b) Colonoscopy showing remission of the rectum.

esophageal ulcer have had other extracolonic manifestations. Various extracolonic manifestations of UC, such as ocular lesions, skin disease, and peripheral arthritis, have been reported (1); however, their causes are currently unknown.

In conclusion, esophageal ulcer associated with UC is extremely rare. In most cases, it may occur as an extracolonic manifestation. The pathological findings of esophageal le-

sion are non-specific for UC. Therefore, a comprehensive diagnosis excluding disorders related to infection and medication is required. UC-associated esophageal ulcers are typically associated with the disease onset or relapse of UC, particularly in younger patients, and the treatment response is fortunately considered good. However, the etiology of esophageal ulcer associated with UC remains unknown.

**Table 1. Clinical Data of UC Patients with Esophageal Ulcer.**

Case (No)	Ref No.	Age (yrs)	Sex	Duration of UC	UC phase	Type	UC treatment
1	Ours	16	F	0	Active	Total	PSL
2	Ours	19	F	0	Active	Total	PSL
3	6	15	M	2 years	Remission	Left side	PSL, SASP
4	7	23	M	5 years	Remission	Total	PSL, SASP
5	8	21	F	0	Active	N/A	PLS, SASP
6		19	M	0	Active	N/A	N/A
7	10	47	F	0	Active	Right side	5ASA
8	4	18	F	7 years	Relapse Active	Total	SASP
9	11	18	M	1 year	Active	Left side	PSL, 5ASA
10	12	19	M	0	Active	Total	none
11	13	51	M	0	Active	Total	PSL, 5ASA
12	14	33	M	0	Active	Total	PSL, LCAP
13	15	52	F	3 years	Relapse Active	Left side	SASP
14	5	28	M	17 years	Post operation	Total	Total colectomy and ileostomy
15	8	26	M	2 months	Post operation	Total	Sbttotal colectomy and ileostomy
16		14	F	5 years	Post operation	Total	Sbttotal colectomy and ileostomy
17		24	M	9 years	Post operation	Total	Total proctocolectomy
18	9	21	M	3 years	Post operation	Total	Total colectomy and ileostomy
19	16	47	M	21 years	Post operation	N/A	Sbttotal colectomy and ileostomy
20		53	M	N/A	Post operation	Total	Sbttotal colectomy

UC: ulcerative colitis, N/A: data not available, PSL: prednisolone, SASP: salazosulfapyridine, 5-ASA: 5-aminosalicylic acid, F: female, M: male

**Table 2. Clinical Data of UC Patients with Esophageal Ulcer.**

Case (No)	Esophageal ulcer (EU)	Location	EU symptoms
1	An esophageal ulcer with aphthae	Middle esophagus	Chest pain
2	Longitudinal oesophageal ulcer	Lower esophagus	Chest pain on swallowing
3	Severe esophagitis	Lower esophagus	Parasternal chest pain and dysphagia
4	Shallow ulceration with gross diffuse irregularity and polyp formation	Middle and lower esophagus	Dysphagia
5	Active ulcerative esophagitis	N/A	N/A
6	Marked ulcerative esophagitis	N/A	Substernal pain and dysphagia
7	Multiple irregular esophageal ulcers	Whole esophagus	Anterior chest pain and dysphagia
8	Longitudinal oesophageal ulcer with haemorrhage	Middle and lower esophagus	Sore throat and pain on swallowing
9	Punched-out esophageal ulcer	Middle esophagus	Sore throat and anterior chest pain
10	Punched-out esophageal ulcer	Middle esophagus	General fatigue
11	Punched-out esophageal ulcer	Middle and lower esophagus	Anterior chest pain on swallowing
12	Punched-out esophageal ulcer	Middle and lower esophagus	Anterior chest pain and dysphagia
13	Punched-out esophageal ulcer	Middle esophagus	Anterior chest pain on swallowing
14	Web formation	Middle esophagus	No
15	Esophageal ulcerations with perforation into the anterior mediastinum	N/A	Dysphagia, fever, hypotension
16	Necrotizing fibrinopurulent ulceration	N/A	N/A
17	Ulcerative and membranous esophagitis	N/A	Nausea, vomiting and hematemesis
18	Multiple friable ulcerations	Whole esophagus	Severe odynophagia and dysphagia
19	Necrosis	Lower esophagus	Epigastric pain
20	Necrosis	Middle and lower esophagus	Hematemesis

UC: ulcerative colitis, N/A: data not available

Since UC has various pathologies, the accumulation of more cases will be necessary to confirm these findings in the future. The two cases reported in the present study also had

atypical aspects and require strict follow-up.

We believe that this case series and literature review will facilitate the accurate and prompt diagnosis of esophageal

**Table 3. Clinical Data of UC Patients with Esophageal Ulcer.**

Case (No)	EU biopsy	EU treatment	Outcome of EU	Other complication
1	Severe inflammatory cell infiltration	PSL	Improvement	No
2	Infiltration of inflammatory cells in the epithelia and no specific information	PSL	Improvement	Oral ulcer
3	Superficial inflammation	PSL	Improvement	Maculopapular eruption
4	Chronically inflamed and edematous, with a dense infiltrate of plasma cells, lymphocytes, and histocytes	PSL	Improvement	Buccal ulceration and arthritis
5	N/A	-	-	No
6	N/A	-	-	Necrotic ulceration in the inguinal, genital regions and lower extremities
7	Nonspecific findings other than inflammatory cell infiltration	5ASA, H2blocker	Improvement	No
8	Nonspecific findings other than inflammatory cell infiltration	PSL	Improvement	No
9	Nonspecific findings (Appearance of regenerative epithelium)	PSL	Improvement	Oral ulcer and pancreatitis
10	Nonspecific findings	PSL, SASP	Improvement	No
11	Thickening of epithelial stratum spinosum without nuclear inclusion body	PPI	Improvement	No
12	Nonspecific findings (Appearance of regenerative epithelium)	PPI	Improvement	No
13	Nonspecific findings other than inflammatory cell infiltration	PSL	Improvement	No
14	N/A	PSL	N/A	Mouth and pyoderma gangrenosum
15	N/A	-	-	Oral ulcerations, pustular dermatitis, arthritis
16	N/A	-	-	N/A
17	N/A	-	-	Ulcer of his buttock, paronychia of hands
18	Dense infiltrate of polymorphonuclear cells, a few eosinophils and mononuclear cells	PSL, tetracycline	N/A	Arthritis, episcleritis, oral ulcerations and erythema nodosum
19	Inflammatory cell and infiltration	PPI	Stricture	No
20	Not examination	PPI	Stricture	No

UC: ulcerative colitis, EU: esophageal ulcer, N/A: data not available, PSL: prednisolone, SASP: salazosulfapyridine, 5-ASA: 5-aminosalicylic acid, PPI: proton pump inhibitor

ulcer associated with UC.

Informed consent was obtained from the patients for the publication of their information and imaging.

**The authors state that they have no Conflict of Interest (COI).**

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