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Original Article

Connective tissue disease-induced gastrointestinal vasculitis: a clinical analysis of 14 cases

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Abstract: Investigate the clinical characteristics of connective tissue disease (CTD) patients with gastrointestinal vasculitis to improve diagnosis and treatment. Retrospective analysis of the clinical presentation, examination, testing, treatment and prognosis from 14 CTD patients with gastrointestinal vasculitis during a 12-years period. All 14 patients had clinical manifestations of gastrointestinal involvement and (or) symptoms. The most common clinical presentation was abdominal pain, followed by hemafecia. Laboratory tests showed positive fecal occult blood in 9 patients. Seven cases underwent endoscopy and nonsurgical medical treatment. Seven patients underwent surgical exploration, and were diagnosed intestinal necrosis in 3 cases, gastrointestinal perforation in 5 cases, peritonitis in 7 cases, intestinal obstruction in 3 cases and gastrointestinal ulcer in 7 cases. Histopathological examination identified significant neointimal hyperplasia, obliteration, and fibrinoid necrosis in the small blood vessels, or thrombosis. Six patients died, 4 during the surgery and 2 cases died during the nonsurgical treatment. CTD patients with gastrointestinal vasculitis showed unspecific symptoms, but had high mortality rate. Early diagnosis and prompt treatment can improve the prognosis. Positive fecal occult blood test can be considered as a warning sign, digestive endoscopy is the most direct method for early diagnosis.

Keywords: Connective tissue diseases, endoscopy, gastrointestinal vasculitis

Introduction

Connective tissue disease (CTD) is characterized with chronic inflammation of blood vessels and connective tissue in pathology. Its clinical manifestations can vary based on the type, size, location and pathological features of the involved blood vessels and vascular lesions can expand to multiple organ systems. Connective tissue disease is an independent risk factor for the inflammation of the digestive tract [1] since vasculitis can cause insufficient blood supply to gastrointestinal wall and subsequently ischemia [2, 3], which if not diagnosed and treated promptly, can progress to gastrointestinal ulcers, bleeding, even life-threatening conditions, such as perforation, enteroplegia, or intestinal infarction [4] that may have case fatality rate of up to 60%~80% [5]. In the management of CTD, this serious complication has drawn attention of clinical researchers. Lee et al. [6] studied the association between activity index of systemic lupus erythematosus (SLEDAI), laboratory test results and incidence of lupus enteritis (gastrointestinal vasculitis), found overall poor correlation and not suitable for early diagnosis. Pagnoux et al [7] studied patients with both systemic vasculitis and gastrointestinal vasculitis, suggested that early nonsurgical treatment and timely surgical intervention can improve prognosis. However, in practice, due to the lack of research on the early presentation of these diseases, misdiagnosis is common [8], which can delay the treatment. Because CTD is generally rare and patients with complications are even more difficult to find, we identified 14 CTD cases with gastrointestinal vasculitis and conducted retrospective analysis of their clinical characteristics, treatment and prognosis, to support the early diagnosis of CTD patients with gastrointestinal vasculitis.

Materials and methods

Study population

Hospitalized CTD patients with gastrointestinal vasculitis from August 2002 to August 2014 in Fuxing Hospital of Capital Medical University in

Table 1. Clinical data of CTD patients with gastrointestinal vasculitis general information and laboratory tests

ID	D	G	A	DOCO	GI Symptoms	Abdominal Signs	ESR	CRP	ANA	ANCA	Fecal OB
1	SLE	F	49	36	Abdominal pain, vomiting, stopping defecation and outgas	Peritoneal irritation sign positive, Hyperactive bowel sound, positive sign of ascites	105	183.2	+	-	NK
2	SLE	F	45	48	Abdominal pain, stopping defecation and outgas	Peritoneal irritation sign positive, Hyperactive bowel sound, positive sign of ascites	81	202.2	+	-	NK
3	RA	F	75	72	Hemafecia	Hyperactive bowel sound	32	80.3	-	-	+
4	Systemic Sclerosis	F	76	0	Abdominal pain	Peritoneal irritation sign positive, positive sign of ascites	56	132	+	-	+
5	Systemic vasculitis	F	40	2	Abdominal pain, stopping defecation and outgas	Hyperactive bowel sound	70	33.1	+	-	NK
6	Systemic vasculitis	F	46	0	Abdominal pain, stopping defecation and outgas	Peritoneal irritation sign positive, Disappearance of bowel sound, positive sign of ascites	30	92.8	-	-	NK
7	Systemic vasculitis	M	49	60	Abdominal pain	Hyperactive bowel sound	21	8.6	-	-	+
8	Systemic vasculitis	F	79	12	Retrosternal pain, dysphagia	Negative	92	112.4	-	+	+
9	Systemic vasculitis	M	81	1	Hemafecia	Negative	56	12.5	+	+	+
10	Sjogren syndrome	F	72	48	Hemafecia (Abdominal pain)	Negative	19	2.8	+	-	+
11	SLE	M	38	0	Abdominal pain, diarrhea	Abdominal tenderness, attenuated bowel sounds	85	28.1	+	-	+
12	SLE	M	56	6	Hematemesis, hemafecia	Abdominal tenderness, Hyperactive bowel sounds	112	60.7	+	+	+
13	Systemic vasculitis	M	72	4	Nausea, vomiting, Abdominal pain, abdominal distension	Peritoneal irritation sign positive, Remote and attenuated bowel sound, positive sign of ascites, abdominal mass	63	153.3	+	+	+
14	Systemic vasculitis	F	53	0	Diarrhea, difficult defecation	Negative	25	3.1	-	-	-

Note: CTD, Connective Tissue Disease; ID, identification; D, disease; G, gender; A, age (year); DOCO, disease onset to complication occurrence (month); ESR, erythrocyte sedimentation rate (mm/1 h); CRP, C-reactive protein (mg/L); ANA, Anti-nuclear antibodies; ANCA, Anti-neutrophil cytoplasmic antibodies; SLE: systemic lupus erythematosus; F, female; +, positive; -, negative; NK, not known; RA: rheumatoid arthritis; ACA: Anti-centromere antibody; M, male.

Beijing, China, who had complete data and confirmed diagnosis, were considered for participation. Inclusion criteria were: A) more than 18 years of old; B) meet the diagnostic criteria for CTD with/out pathologic confirmation; C) hospitalized for gastrointestinal vasculitis with complete data. Exclusion criteria were the presence of: A) intestinal infectious diseases; B) atherosclerosis of abdominal aorta, mesenteric artery; C) gastrointestinal tumors; D) primary hypertension and/or coronary artery disease and/or diabetes, complicated with ischemic enteritis. According to the eligibility criteria, 14 cases were consecutively enrolled. The study was approved by the ethics committee of Fuxing Hospital. And informed consents were obtained from the patients or their families.

Retrospective study

Information collected from each patient included: 1) clinical presentation of gastrointestinal symptoms at admission; 2) results of laboratory test at admission: routine stool test, erythrocyte sedimentation rate(ESR), C-reactive protein (CRP), blood clotting tetrachoric and autoimmune antibody; 3) treatment: depending on the severity, patients either underwent abdominal surgery due to acute abdomen at the time of admission, or received nonsurgical treatment along with gastroscopy and/or colonoscopy; 4) results of surgery/endoscopy; 5) results of pathological examination post-surgery or endoscopicbiopsy; 6) follow up: patients were followed outpatient at the time of discharge, 3, 6, 12 months after discharge for disease progression. The results were analyzed with statistical description.

Results

General information

Of 14 cases, 9 were females, 5 were males. Age spanned from 38 to 84 years, with a mean of 59 years. The duration from CTD onset and occurrence of gastrointestinal symptoms was between 0 to 72 months, average 20.6 months (**Table 1**).

Composition of the CTD cases

This CTD case series consisted of 4 cases of systemic lupus erythematosus (SLE), 1case of rheumatoid arthritis (RA), 1 case of Sjogren's syndrome, 1 case of systemic sclerosis, and 7 cases of systemic vasculitis. SLE and RA patients were diagnosed in accordance with the American College of Rheumatology (ACR) 1997classification criteria for SLE [9], and 1987 diagnostic criteria for RA [10], respectively. The patient with Sjogren's syndrome also met International 2002 Classification of Sjogren's syndrome diagnostic criteria [11]. Patients with systemic vasculitis were diagnosed based on criteria for classification of vasculitis established in 1993 at Chapel Hill conference [12]. Patient with systemic sclerosis met the diagnostic criteria established in 1980 by Masi et al [13].

Clinical presentation

All 14 patients had clinical symptoms and (or) signs of gastrointestinal involvement, including: abdominal pain in 9 cases, hemafecia in 4 cases, stop of outgas and defecation in 4 cases, nausea/vomiting in 2 cases, diarrhea in 2 cases, and 1 case of dysphagia (**Table 1**).

Laboratory tests

All 14 patients had elevated inflammatory markers: ESR 19~112 mm/1 h, with a mean of 60.5 mm/1 h; CRP 2.8~202.2 mg/L, with a mean of 8.93 mg/L. They had positive antinuclear antibodies (ANA) in 9cases, anti-neutrophil cytoplasmic antibodies (ANCA) in 4 cases, anti-centromere antibody (ACA) in 1 case. Also, 1 patient had positive rheumatoid factor (RF), Anti-perinuclear factor (APF) and Anti-keratin antibody (AKA). Anti cardiolipin antibodies (ACL) were negative and coagulation test was normal for all patients. Fecal occult blood test was positive in 9 cases (**Table 1**).

Diagnosis

At the time of admission, the diagnosis was gastrointestinal bleeding in 4 cases, esophagitis in 1 case, diarrhea, colitis in 2 cases, intestinal obstruction in 1 case, acute abdomen in 5 cases, and pancreatitis in 1 case. Seven cases underwent surgery; the other 7 cases received nonsurgical treatment (**Table 2**).

Endoscopy and surgery

Endoscopy and surgery identified intestinal necrosis in 3 cases, gastrointestinal perfora-

Table 2. Clinical data of CTD patients with gastrointestinal vasculitis treatment, diagnosis and prognosis

ID	Diagnosis	Surgical/endoscopy-diagnosis	Pathology	Prognosis			
				Discharge	3 m	6 m	12 m
1	Acute abdomen	(Surgery) ileum necrosis and perforation, Peritonitis	Intestinal wall tissue bleeding and necrosis, neutrophil infiltration around small blood vessels in intestinal wall (vasculitis), fibroid necrosis of small blood vessels, thrombosis in mesentery veins	Died	×	×	×
2	Acute abdomen	(Surgery) ileum necrosis and perforation, Peritonitis	Severe dysaemia in intestine and mesentery, extensive hemorrhagic necrosis of intestinal wall, thrombosis in mesentery veins	Survival	Recurrent, died during surgery	×	×
3	Digestive tract hemorrhage	(Surgery) Stricture of transverse colon, Intestinal obstruction, peritonitis	Vasculitis of small blood vessels in the intestinal submucosa. Fibrinoid necrosis of small blood vessels, unclear structure, a large number of inflammatory cell infiltrations.	Survival	Survival	Survival	Survival
4	Acute Abdomen	(Surgery) ileum perforation, Peritonitis	Intestinal wall extensive hemorrhage and necrosis. Epithelial necrosis, vasculitis of small blood vessels in submucosa. Fibrinoid necrosis of small blood vessels, a large number of inflammatory cell infiltrations.	Died	×	×	×
5	Intestinal Obstruction	(Surgery) Stricture of descending colon, intestinal obstruction, peritonitis	Vasculitis of small blood vessels in small intestine, thrombosis.	Survival	Survival	Survival	Survival
6	Acute Abdomen	(Surgery) Necrosis and perforation of jejunum, acute pancreatitis, thrombus in portal vein and splenic vein, peritonitis	Sectional mesenteric vein thrombosis, reactive lymphoid hyperplasia, infiltration of lymphocytes in adipose tissue, the majority of intestinal mucosal congestion, hemorrhage and necrosis	Died	×	×	×
7	Acute Abdomen	(Surgery) stricture of ileum, peritonitis	Massive neutrophil infiltration in perivascular tissue of the intestinal wall (vasculitis), fibrinoid necrosis of small blood vessel, thrombosis.	Survival	Survival	Survival	Survival
8	Esophagitis	(Endoscopy) esophageal ulceration, esophagotracheal fistula	Chronic Esophagitis and ulceration, a large number of plasma cells infiltration, under magnification neutrophil infiltration in the blood vessel wall (vasculitis) was changed. No abnormal cells.	Survival	Survival	Died of malnutrition, lung infection	×
9	Digestive tract hemorrhage	(Endoscopy) Stomach, Duodenum ulcers	Mucosal shedding, ulceration, fibroid necrosis of the small blood vessels submucosa, neutrophil infiltration	Survival	Recurrent Hemafecia, Survival	Survival	Survival
10	Digestive tract hemorrhage	(Endoscopy) Colonic ulcer	Vasculitis of small blood vessels in the intestinal submucosa. Fibrinoid necrosis of small blood vessels, a large number of inflammatory cell infiltrations. Thrombosis.	Survival	Intermittent abdominal pain, Survival	Survival	Survival
11	Diarrhea	(Endoscopy) Stomach, Colonic ulcers	Chronic inflammation of the mucosa, submucosal erosion or necrosis, visible inflammatory cell infiltration, including hemosiderin cells, fibroid necrosis of small blood vessels in the intestinal wall.	Survival	Survival	Survival	Survival
12	Digestive tract hemorrhage	(Endoscopy) Stomach, Duodenum ulcers, Colitis in ileocecal junction	Mucosal shedding, ulceration, fibroid necrosis in part of the small blood vessels in submucosa, neutrophil infiltration	Survival	Survival	Survival	Survival
13	Acute pancreatitis	(Endoscopy) Stomach, Duodenum ulcers	Chronic inflammation and ulceration, neutrophil infiltration in the blood vessel wall of submucosa.	Died	×	×	×
14	Colitis	(Endoscopy) Deep and large Sigmoid ulcer	(Colon) mucosal shedding, ulceration, a large number of inflammatory cell infiltration in blood vessel walls, significant intimal hyperplasia significantly, obliteration	Survival	Survival	Survival	Survival

Note: CTD, Connective Tissue Disease; ID, identification; ×, not data.

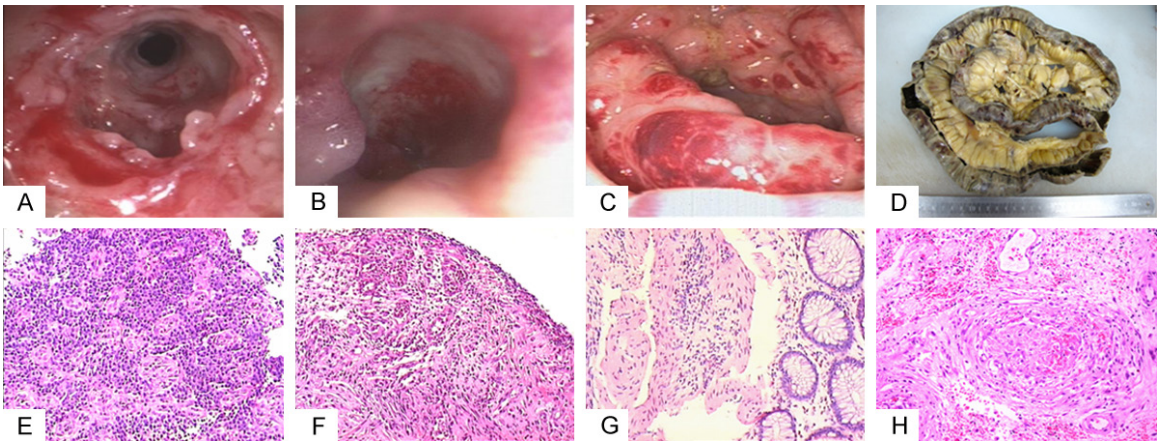

Figure 1. Endoscopic/Surgical findings and corresponding pathology. A: Gastroscopy: significantly worse esophageal mucosal hyperemia, edema and erosion, significant lumen stenosis, endoscopy could not pass. B: Gastroscopy: an enormous ulcer at duodenal ampulla, rough bottom, covered by white membrane, hyperemia and edema of surrounding mucosal tissue, and poor elasticity of biopsy specimen. C: Colonoscopy: varying degrees of edema in colonic mucosa, erosion or ulceration of mucosal tissue, ulcers mostly longitudinal or irregular in shape, clear boundaries between lesions and normal mucosa. D: Small intestine gross image: intestinal bleeding and necrosis (dark red), pale yellow purulent exudate on serosa (surface) of small intestine. E: (Pathology for A, esophagus) Acute, chronic inflammation and ulceration of esophageal tissue, a large number of plasma cells, neutrophil infiltration in the blood vessel wall under magnification, characteristics of vasculitis. F: (Pathology for B, stomach) Ablation of stomach mucosa, ulceration, fibroid necrosis of some small blood vessels in the submucosa, neutrophil infiltration. G: (Pathology for C, colon) Significant neointimal hyperplasia, obliteration of lumen. H: (Pathology for D) HE staining showed vasculitis in small intestinal wall, thrombosis.

tion in 5 cases, peritonitis in 7 cases, intestinal obstruction in 3 cases, gastrointestinal ulcer in 7 cases, and pancreatitis in 2 cases. Of14 patients, 1 case involved esophagus, 4 cases involved stomach and duodenum, 6 cases involved small intestine, and 6 cases involved colon (**Figure 1**; **Table 2**).

Pathological examination

Vasculitis was confirmed in 7 cases by gastrointestinal endoscopic biopsy and the other 7 cases through pathology examination of post-surgical specimens. Histological exam showed massive neutrophil infiltration in small blood vessel wall of the digestive tract in all patients, suggesting vasculitis as the cause, and significant intimal hyperplasia, obliteration or disappear of lumens, as well as fibrinoid necrosis of the small blood vessels. There was also thrombosis formed as the result of inflammatory vascular necrosis in 5 cases. Of them, 4 patients had intestinal necrosis and intestinal perforation (**Figure 1**; **Table 2**).

Prognosis

Four patients died during the hospitalization: 3 in surgery group and 1 in nonsurgical group. Three months after discharge, one case died from mesenteric venous thrombosis and 6monthsafter discharge, another case that received nonsurgical treatment and suffered dysphagia due to esophageal fistula also died from lung infections and malnutrition. Eight patients were still alive at 12-month visit post-discharge, including 3 from surgical group and 5 from nonsurgical group (**Table 2**).

Discussion

In this study, abdominal pain is the main clinical presentation, consistent with other studies in the literature that studied the gastrointestinal manifestations of systemic vasculitis [7] and localized gastrointestinal vasculitis [14], and the symptoms lack specificity. However, from the laboratory test results, the rate of positive fecal occult blood was significantly higher than gastrointestinal bleeding (9/14 vs. 4/14, respectively), suggesting the importance of stool test and fecal occult blood could be positive in early stage of gastrointestinal vasculitis.

In this study, gastrointestinal manifestations of vasculitis commonly involve the small intestine and colon, can affect multiple organs simulta-

neously. Intestinal necrosis is the main representation of intestinal involvement, and the involvement of colon can present as mucosal erosions, ulcers with bleeding. Ulcer is also the main presentation of upper gastrointestinal involvement. The literature [15] reported CTD-induced gastrointestinal vasculitis can affect the esophagus, stomach, duodenum, jejunum, ileum, transverse colon and descending colon. When the gastrointestinal system is involved, the characteristics of clinical symptoms are associated with the size of blood vessel lesion. Large vessel vasculitis causes sectional intestinal ischemia or infarction; vasculitis of middle size vessel leads to smaller scale of bleeding and infarction; while vasculitis of small vessel only causes tissue inflammation and capillary hemorrhage.

Pathology of 14 cases in this study showed that vasculitis of blood vessels supplying the digestive tract is the cause of the complication, and once the disease progresses, vascular obliteration, thrombosis can occur and patients' prognosis was poor. A French study of 278 patients with nodular nodosa/Churg-Strauss syndrome and microscopic polyarteritis reported death in 85 cases, 10% of which were due to intestinal infarction [16]. In this study, 6 out of 14 patients died, suggesting a high case fatality rate. Guillevin L et al. [17] conducted a cohort study of 1108 systemic vasculitis patients in France, found that gastrointestinal involvement was the main reason for the decline of 5-year survival rate (others included: >65 years, cardiac symptoms, renal insufficiency), with an incidence rate of 25.7% and hazard ratio of 1.5 ($P<0.01$).

In this study, patients who received nonsurgical treatment were diagnosed relatively early, had milder symptoms; while all patients undergone surgery had acute abdomen and underwent emergency surgery, thus was diagnosed late. Severe condition is the main reason for higher mortality in the surgical group. Another study by Guillevin et al. [18] followed 342 patients with nodular nodosa/Churg-Strauss syndrome prospectively, and found that the relative risks of mortality for patients with severe gastrointestinal symptoms or undergone gastrointestinal surgery were 3.13 ($P<0.0001$) and 2.83 ($P<0.008$) respectively. Multivariate analysis showed that the complication of gastrointestinal bleeding, perforation, infarction or pancreatitis were all associated with poor prognosis ($P<0.001$). Paqnoux C [7] analyzed the data from 62 systemic vasculitis patients with gastrointestinal involvement and found that the 10monthsand 5-yearsurvival rates for 21 patients undergone surgical treatment were 71% and 56%, respectively, and 94% and 82%, respectively for the 41 cases received nonsurgical therapy. Several case reports also indicated that with timely and accurate diagnosis, conservative nonsurgical treatment can achieve satisfactory results, without recurrence after more than two years of follow-up [19].

For patients with vasculitis involving the gastrointestinal tract, how can we provide early diagnosis and timely nonsurgical treatment? Currently the most direct way is pathological exam of specimens collected from digestive endoscopy. In this study, patients who did not undergo surgery were diagnosed by digestive endoscopy, and received timely medical treatment, thus the fatality rate (2/7) was lower than those undergone surgery (4/7). Since this study only had very limited number of patients, we cannot make confirmative conclusion on the mortality. We also reviewed the literature and did not find relevant report. Beppu K et al. [20] retrospectively studied the association between endoscopic findings and clinical severity of ischemic colitis among 106 patients, found that CTD is an independent factor for severe ischemic colitis ($P<0.05$). Within 3 days of gastrointestinal symptoms (abdominal pain, diarrhea, changes of bowel movement and blood stool) onset, colonoscopy could reveal the severity and patients' prognosis.

In conclusion, based on our clinical observations, CTD patients with gastrointestinal vasculitis can present with various symptoms. Positive occult blood test can be used as a warning sign, and should be given enough attention. Vasculitis may involve the entire digestive tract; symptoms may be associated with the size of lesion vessel. Vasculitis of large vessel can cause sectional intestinal ischemia or infarction; vasculitis of middle size vessel can lead to smaller scale of bleeding and infarction; while vasculitis of small vessel only causes tissue inflammation and capillary hemorrhage. As the disease progresses, lumen obliteration and thrombosis can occur. The case fatality rate is high, early diagnosis and prompt treat-

ment can improve the prognosis. Digestive endoscopy is still the most direct method for early diagnosis in practice. Because of the limited number of cases in our study, we can only provide a descriptive analysis, and additional cases are needed to provide more confirmative results.

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Disclosure of conflict of interest

None.

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