Case Report

Delayed Relapse of Churg-Strauss Syndrome Manifesting as Colon Ulcers with Mucosal Granulomas: 3 Cases

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ABSTRACT. Churg-Strauss syndrome (CSS) is characterized by small vessel vasculitis and extravascular granulomas. The American College of Rheumatology classification criteria for CSS include asthma, eosinophilia, and clinical manifestation of vasculitis. Gastrointestinal (GI) manifestations occur in 30% of patients, but are inaugural in only 16%. They denote vasculitis of the stomach and small bowel wall, and consist in protean, nonspecific pain. GI involvement is of adverse prognostic significance in CSS. Ulcer formation in the GI tract mucosa is a rarer manifestation, usually discovered upon laparotomy or autopsy. We describe 3 new cases of colonic ulcers in CSS. Unusual features were diagnosis of the ulcers during a delayed relapse and presence of eosinophilic granulomas within the mucosa. (J Rheumatol 2002;29:388–91)

Key Indexing Terms:
CHURG-STRAUSS SYNDROME
COLON ULCER
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Churg-Strauss syndrome (CSS), first described in 1951, is characterized by small vessel vasculitis and extravascular granulomas. The American College of Rheumatology (ACR) classification criteria[1] for CSS include asthma, eosinophilia, and clinical manifestation of vasculitis.

Gastrointestinal (GI) manifestations occur in 30% of patients, but are inaugural in only 16%[2]. They denote vasculitis of the stomach and small bowel wall, and consist in protean, nonspecific pain. GI involvement is of adverse prognostic significance in CSS[2].

Ulcer formation in the GI tract mucosa is a rarer manifestation, usually discovered upon laparotomy or autopsy[3]. A few cases diagnosed by endoscopy have been reported recently, mainly by Japanese authors[3-7]. The ulcers were usually present at the diagnosis of CSS and selectively involved the stomach and small bowel. Histology showed nonspecific vasculitis without eosinophils[3].

We describe 3 new cases of colonic ulcers in patients with CSS. Unusual features were diagnosis of the ulcers during a delayed relapse and presence of eosinophilic granulomas within the mucosa.

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CASE REPORTS

Case 1. A 45-year-old woman was admitted in 1996 for abdominal pain. At 30 years of age, she had received a diagnosis of CSS based on airway disease, eosinophilia, and vasculitis. Her symptoms at the time included recent onset steroid dependent asthma, allergic rhinitis of 4 years' duration, a pleural exudate (44 g/l protein and 1100 eosinophils/mm^3), radiological signs of interstitial lung disease, and lung function testing evidence of airway obstruction. The symptoms of vasculitis consisted of fatigue, weight loss, sublingual ischemic lesions, subcutaneous nodules, and inflammatory polyarthralgia. Repolarization disorders and uncomplicated pericarditis were present from the outset. Blood test showed a high eosinophil count (3000/mm^3), erythrocyte sedimentation rate (ESR) 120 mm/h, white blood cells (WBC) 12,500/l, and an elevated IgE titer. Biopsy of a subcutaneous nodule revealed necrotizing vasculitis with an eosinophilic granuloma, confirming the diagnosis of CSS. Glucocorticoid therapy (prednisone 1 mg/kg/day increased to 20 mg) and azathioprine (2 mg/kg/day) were given from 1983 to 1996. Her respiratory, cutaneous, and cardiac symptoms resolved. However, she had persistent asthma requiring daily prednisone (20 mg), and her eosinophil count was 768/mm^3 in March 1996 and ESR 20.

Her first abdominal symptom was a self-limited episode of abdominal pain in 1984. In 1996, abdominal pain, diarrhea, tenesmus, and fatigue prompted an inpatient evaluation. Body temperature was 38°C. The eosinophil count was 4300/mm^3, WBC 15,000/mm^3, and ESR 90 mm/h. Colonoscopy examination showed ulcers extending along the entire colon but sparing the terminal ileum (Figure 1). Ulcers were small, fibrinous, superficial in mucosa surrounded by an erythematous rim. Upper endoscopy was normal. Biopsies of an ulcer in the sigmoid colon disclosed colitis with eosinophilic infiltrate and vasculitis (Figure 2). Concomitant abnormalities included peripheral demyelinating, sensory and motor neuropathy on electromyographic examination, without symptoms, and a moderate decline in myocardial function, with septal hypokinesis and a decrease in ejection fraction to 40%.

Six methylprednisolone boluses (once monthly, 1000 mg each) were given to curb the high disease activity. The pain resolved promptly. Methylprednisolone was replaced by oral glucocorticoid therapy in decreasing doses. Eleven cyclosphosphamide boluses (750 mg/m^2/mo)

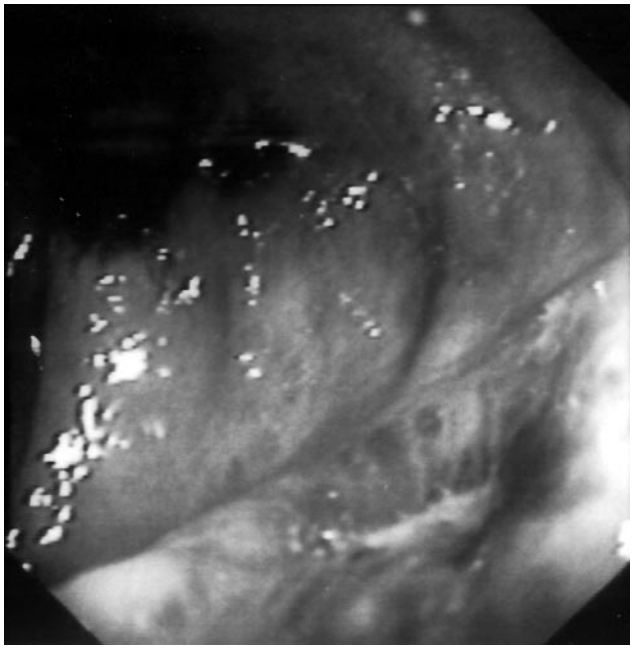

Figure 1. Patient 1: Colonic ulcer, endoscopic view.

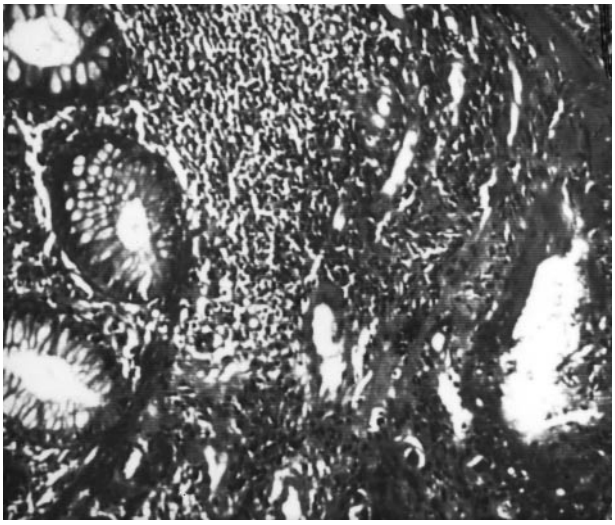

Figure 2. Patient 1: Colonic ulcer. Histological examination reveals diffuse eosinophilic infiltrate and vasculitic aspects of small vessels (May Grunvald Giemsa stain; original magnification ×50).

were also given, the last being in March 1998. Followup endoscopy after one month and 12 months showed healing of the ulcers and clearing of the eosinophilic infiltrate. Myocardial function remained stable and the neurological abnormalities on electromyogram resolved. Five years later, the only symptom is allergic rhinitis, and treatment is 8 mg prednisone per day.

Case 2. A 50-year-old man was admitted twice in 1996 for abdominal symptoms and fever. CSS had been diagnosed when he was 27 years of age. At the time, he had a one year history of steroid dependant asthma with fever and debilitation unresponsive to antituberculous therapy. Vasculitis symptoms included inflammatory polyarthralgia, lower limb purpura, hemoptysis, and skin nodules. The eosinophil count was 7000/mm^3. A muscle biopsy disclosed focal necrotizing arteritis and an eosinophilic infiltrate. Glucocorticoid therapy in a dose of 2 mg/kg/day tapered to 5 mg/day was given, in combination with 6 cyclophosphamide boluses. The symptoms of vasculitis abated, with the exception of intermittent abdominal and testicular pain. The eosinophil count and inflammation measures returned to normal. Steroid dependent asthma requiring 5 mg/day prednisone persisted.

In 1996, acute febrile peritonitis due to perforation of a colonic diverticulum required an emergency left hemicolectomy. Histology showed diverticulitis. WBC count was 17,500/mm^3 and *Clostridium difficile* and stool culture were negative a few months later, bloody diarrhea occurred, with fever, fatigue and 5 kg weight loss, and arthralgia. Laboratory tests showed ESR 80 mm and eosinophilia 6810/mm^3. Colonoscopy examination showed mucosal erythema and multiple small superficial fibrinous ulcers. Biopsies of the ulcers disclosed ischemic proctitis, vasculitis, and an eosinophilic infiltrate. Bronchoalveolar lavage contained 350,000 cells/ml with 80% eosinophils and no microorganisms. Glucocorticoid therapy (1 mg/kg/day) and 6 new cyclophosphamide boluses for 6 months were given. The intestinal symptoms resolved and a followup rectoscopy was normal. Two years later the treatment is 5 mg prednisone per day.

Case 3. A 45-year-old woman was admitted in 1994 for acute abdominal symptoms. She had had asthma at 12 years of age, with a favorable outcome after hyposensitization. However, severe symptoms of steroid dependent asthma developed when she was 25 years of age. Radiographs showed a lung infiltrate. Additional manifestations were allergic rhinitis, fever, debilitation, and vasculitis responsible for inflammatory polyarthralgia, diffuse purpura, mononeuritis confirmed by electromyography, and a type I atrioventricular block. Blood tests showed eosinophilia (3200/mm^3), WBC 10,500/mm^3, and IgE elevation (1100 IU/ml). Necrotizing vasculitis and an eosinophilic infiltrate were revealed by a skin biopsy, confirming the diagnosis of CSS. To curb the severe clinical manifestations, glucocorticoid therapy was given (1 mg/kg/day) and 13 plasma exchanges were performed, with good effect on the clinical, laboratory, electromyographic, and electrocardiographic abnormalities. Steroid dependent asthma persisted, requiring 15 mg/day prednisone.

In 1994, abdominal pain, bleeding per rectum, and diarrhea with mucus and blood prompted an evaluation. Upper endoscopy was normal. Colonoscopy examination showed proctitis and sigmoiditis, with small superficial ulcers with no fibrinous exudate. At histology, a polymorphic infiltrate predominantly composed of eosinophils was seen in the mucosa. The clinical outcome was favorable, with no other evolution 6 years after the initial relapse, after an increase in the prednisone dosage to 1 mg/kg and local mesalazine therapy.

DISCUSSION

Gastrointestinal involvement is common in CSS, with variations across studies (from 17 to 92% of cases), and it has been reported to inaugurate CSS in 13.2% of patients[2]. In the most recent series, Guillevin, *et al*[2] found that 33.3% of 96 patients had abdominal symptoms, which were nearly always present at the diagnosis of CSS. The few available histologic studies[5] showed necrotizing vasculitis of the digestive tract wall. In some cases an eosinophilic infiltrate antedated or accompanied the vasculitis[5]. Nonspecific abdominal pain was the most common clinical symptom. Diarrhea was recorded in one-third of patients[2], whereas bleeding was rare[5].

Guillevin, *et al*[2] obtained strong evidence that GI involvement is an independent indicator of poor prognosis in CSS: in their multivariate analysis, survival after 78 months was significantly lower in patients with than in those

without GI involvement (65 vs 85%). The difference in mortality became significant within the first 2 years after the diagnosis, indicating that GI involvement should be looked for routinely. GI involvement was the primary cause of death in 8% of the patients[2] and came in fourth place among causes of death. Mesenteric infarction[2] and intestinal obstruction with perforation[8] have been the most common intestinal causes of death. GI involvement is among the 5 factors in the Five Factors Score used to evaluate the prognosis of necrotizing vasculitis due to any cause[9].

Ulcers of the GI mucosa have been reported rarely in CSS. Most cases occurred in Japan[3,8,10], where GI involvement seems particularly common for reasons that remain unexplained. The diagnosis was often made upon laparoscopy or autopsy: this was the case, for instance, for 29 of the 34 ulcer episodes in 21 patients reviewed by Shimamoto, *et al*[3]. In many cases, the ulcers were discovered after bowel wall perforation had occurred[3] as a result of mucosal ulceration and transmural necrosis. More recently, cases of uncomplicated ulcers diagnosed by endoscopy have been reported[3,4]. The ulcers were located within and under the mucosa[3,4,8], and were usually multiple[3,4,6,10] and of variable size[3,10], covered by a whitish exudate, and surrounded by an erythematous rim[3,5]. The surrounding mucosa was erythematous. The stomach, duodenum, and jejunum were the most common sites of involvement[3,7,10], with 27 among the 34 ulcer episodes in the Japanese literature reviewed by Shimamoto, *et al*[3]. Fewer than 15 cases with ulcers in the rectum and/or colon have been reported[3,4,6,7,10]. Nonspecific abdominal pain with diarrhea was the most common presentation[3,4,10]. Bleeding was rare[5] and perforation common[3,10]. In every case, the rectal and/or colonic ulcers were present at the diagnosis of CSS[3,4,6-8,10]. A single patient[6] had a 3 year history of purpuric colitis, with mucosal inflammation and infiltration by neutrophils and eosinophils.

The patients with rectal and/or colonic ulcers had severe CSS with numerous signs of extraintestinal vasculitis, including cardiac[6] and neurological[3,4,10] abnormalities. There were histories of asthma of 2 to 5 years' duration, and blood eosinophil count at diagnosis ranged from 1640[5] to 12,300[10] per mm^3.

In most of the anecdotal reports of rectal and/or colonic ulcers, the clinical manifestations[3,4,7,10] and endoscopic lesions[3,4] resolved under glucocorticoid therapy. Shimamoto, *et al*[3] supply no outcome data in the review. Relapses have been reported within the first 6 months of glucorticoid tapering[4-6]. Complications, all of which occurred in Japanese patients, consisted mainly of perforation[3,5,10], which was most common in patients with small bowel involvement. One case of stricture due to an annular ileal ulcer has been reported[8]. In most patients, histology showed nonspecific GI vasculitis[3]. Extravascular granulomas were infrequent[4], and eosinophilic infiltrates exceedingly uncommon. However, eosinophilic infiltrates were often found in the patients with stricture or perforation of the bowel[8,10].

Our 3 cases of intestinal ulcers in patients with CSS exhibit a number of unusual features. First, in all 3 patients the ulcers developed during a delayed relapse of CSS, 13 to 21 years after the diagnosis. Initially no colonoscopic examination was performed because episodes of pain in 2 of our patients were self-limited, without bleeding stool, and at the time colonoscopic examination was not available. In contrast, in all 3 cases, the intestinal symptoms revealing the colonic ulcers were the earliest manifestations of a delayed relapse that occurred after more than 10 years of successful control of the vasculitis. The second unusual feature is the location of the ulcers in the colon (and rectum in 2 cases) in the absence of small bowel involvement on upper endoscopy in 2 patients. Third, colonoscopic examination supplied the diagnosis in all 3 cases and caused no complications. Our 3 cases draw attention to the possibility of colonic ulcer formation and to the value of colonoscopic examination for diagnosis when patients have persistent pain and/or bleeding stool and/or diarrhea. It is important that clinical or biological manifestations of enteric disease were noted in none of our patients, and that the small bowel was not explored. Thus we cannot firmly rule out asymptomatic small bowel involvement.

Our 3 patients had a favorable outcome with glucocorticoid therapy, combined in 2 cases with immunosuppressive therapy and in one with plasma exchanges. Mean followup was 5 years, during which time no relapses occurred. There were no complications due to the ulcer. In case 2, peritonitis caused by perforation of a diverticulum occurred a few months before the intestinal relapse of CSS. However, it is unlikely that the vasculitis contributed to this event since the histological study showed typical diverticulitis with no evidence of vasculitis.

The intestinal symptoms consisted of nonspecific persistent abdominal pain and diarrhea in all 3 patients. Intestinal bleeding, a rarely reported manifestation, occurred in 2 patients.

The histological findings are of great interest — an eosinophilic infiltrate was found in all 3 patients. Two had vasculitis and granulomas. Presence of an eosinophilic infiltrate has been reported very rarely in the literature and supports a possible pathogenic role for intramucosal eosinophils in the development of bowel wall ulcers.

We describe 3 new cases of intestinal ulcers in Churg-Strauss syndrome, which are of particular interest on 3 accounts. First, they show that colonic involvement can be the only manifestation of CSS, although few such cases have been reported. Second, they are to our knowledge the first reported cases in which colonic ulcers were the inaugural manifestation of a delayed relapse, occurring 13 to 21 years after the diagnosis of CSS. Third, histological studies

disclosed not only vasculitis but also granulomas in 2 cases and eosinophilic infiltrates in all 3 cases. Also noteworthy is the good prognosis of this type of gastrointestinal involvement. Thus a colonoscopic examination must be considered in patients with CSS when they have persistent abdominal pain, diarrhea, and/or bleeding stools.

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