Wegener's Granulomatosis with Relapsed Bleeding of Gastric Ulcers: A Case Report

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We treated a 55-year-old male patient with Wegener's granulomatosis (WG) associated with frequent gastric bleeding from multiple ulcerative lesions. Only a few cases of frequent hemorrhaging of peptic ulcers associated with WG have been reported. In our case, a gastric biopsy showed mononuclear cell infiltration in the submucosal area, without granulomas or vasculitis. An endoscopic maneuver, as well as administration of immunosuppressive agents, combined with an H2 receptor antagonist and proton pump inhibitor successfully eliminated the gastrointestinal bleeding.

In this case, proof that the gastrointestinal involvement was pathologically related to WG could not be demonstrated because neither granulomas nor vasculitis were observed in the insufficient biopsy specimen of the stomach. It is also possible that the uremic state and cytotoxic agents worsened the gastrointestinal involvement. However, immunosuppressive therapy combined with routine antilucer treatment was very effective in repairing the ulcerative lesions. The gastrointestinal involvement was considered a possible complication of the WG.

(Key Words: gastric ulcer, gastrointestinal bleeding, vasculitis, Wegener's granulomatosis)

INTRODUCTION

Wegener's granulomatosis is known to be associated with nasal, pulmonary and renal lesions, characterized not only by granulomas in the nose and the lungs, but also by rapidly progressive glomerulonephritis (RPGN). However, there are few reports of frequent gastrointestinal bleeding of peptic ulcers as a complication. Moreover, gastrointestinal granulomas or vasculitis have rarely been reported to be associated with WG.

We report here our experience with a made patient with WG associated with repeated gastrointestinal bleeding which we treated by endoscopic procedures and the administration of an H2 receptor antagonist, proton pump inhibitor, prednisolone and cyclophosphamide. The cause of the pathologic bleeding could not be determined. A biopsy specimen of the stom-ach showed mononuclear cell infiltration in the submucosa without vasculitis or granuloma. Whether or not the pathogenesis of gastric ulcers was associated with WG is discussed.

CASE REPORT

A 55-year-old man complained of high fever, nasal discharge, nasal obstruction, and sore throat since January 14, 1994. Since the symptoms seemed to be those of a common cold, he consulted a local doctor who prescribed NSAIDs (non-steroidal anti-inflammatory drugs) and antibiotics. However, he did not show improvement but actually became worse. He then consulted a otorhinolaryngologist because he also had upper respiratory tract symptoms, including nasal bleeding and obstruction, and underwent a biopsy of the maxillary sinuses because of an abnormal shadow in an X-ray examination. WG was sus-

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Fig. 1-a, 1-b  Granuloma in the nasal cavity. Both foreign body and Langhans' type giant cells are seen. (1-a, HE stain, ×100) Necrotic tissue is observed, but no apparent vasculitis is seen. (1-b, HE stain, ×50)

pected histologically (Fig. 1-a and 1-b). He was referred to ENT (Ear, Nose and Throat) in the Tokai University Hospital, and admitted on February 15, 1994. Laboratory tests on admission revealed progressive renal dysfunction, and he was referred to nephrology immediately. His serum creatinine level rose from 2.4 to 6.8 mg/dl in one week, indicating a RPGN (rapidly progressive glomerulonephritis) syndrome.

Hypertension and gastritis were recorded in his past history, but no medication had been
prescribed. Vital signs on admission included a body temperature of 38.0°C, heart rate of 84 per minute with sinus rhythm and blood pressure of 132/70 mmHg. Physical examination revealed anemic palpebral conjunctivae and coarse crackles in the right upper lung. Erosion and scabs were recognized in his nasal mucous lesion, but lymph node swelling, skin lesions, or edema were not found. No abnormality was seen in his heart and abdomen.

Laboratory findings were as follows: white blood count, 10500/μl; hemoglobin, 8.4 g/dl; hematocrit, 25.4%; blood urea nitrogen, 53.7 mg/dl; serum creatinine, 6.8 mg/dl; uric acid, 7.5 mg/dl; albumin, 2.7 g/dl; C-reactive protein (CRP), 23.7 mg/dl; erythrocyte sedimentation rate (ESR), 146 mm/hr; total cholesterol, 96 mg/dl; and triglyceride, 90 mg/dl. Prothrombin time and partial thromboplastin time were prolonged (PT, 13.9 sec; PTT, 62.7 sec). The serum level of C (protease-3) anti-neutrophil cytoplasmic antibody (C-ANCA) was elevated. Urinalysis revealed 3+ occult blood and 2+ protein (0.45 g/day). Chest X-ray indicated a solitary, vague, rough-shaped and tuberous shadow in the right upper lung field, which was considered to be compatible with WG (Fig. 2).

The clinical course is depicted in Fig. 3. He was placed on hemodialysis immediately after admission because his serum creatinine level exceeded 10.0 mg/dl. Oral administration of cyclophosphamide (CY, 100 mg/day) and prednisolone (PSL, 40 mg/day) were started for WG. Steroid pulse therapy (methylprednisolone, 1,000 mg x 3 days) was also performed. However, massive hematemesis and melena emerged 5 days after the start of treatment. Before this episode, two days earlier, gastroscope showed one ulcer in the active stage, another ulcer in the healing stage, and many hemorrhagic spots (Fig. 4). A biopsy revealed mononuclear cell infiltration in the submucosal area, but neither granuloma nor vasculitis were observed in the specimen (Fig. 5). A gastroendoscopic examination on the day of the gastrointestinal bleeding demonstrated multiple gastric ulcers (Fig. 6). Although injection of ethanol was used to treat the gastric ulcers, this method was not very effective because the ulcers frequently relapsed at the sites of injection for more than 1 month (Fig. 7). The lesions spread to various sites of the stomach. Clipping stopped the bleeding, and medication, including an H2 receptor antagonist and proton pump inhibitor, improved healing of

Fig. 2 Chest x-ray on admission. The shadow in the right upper lung field is solitary, vague, rough-shaped and tuberous. Its features were considered compatible with a granulomatous lesion. It disappeared soon after starting immunosuppressive therapy.
Clinical Course K. S. 55y. o.

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<th>Prednisolone</th>
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Fig. 3 Clinical course. The level of serum creatinine improved in response to immunosuppressive agents (prednisolone and cyclophosphamide). The frequent recurrence of gastrointestinal bleeding was alleviated by a combination of endoscopic procedures, H₂ receptor antagonist, proton pump inhibitor, and immunosuppressive treatment.

Fig. 4 Endoscopic findings (Before gastrointestinal bleeding.) Two gastric ulcers (active and healing stages) were seen. This figure shows the active stage ulcer. It seems that ulcers were already present at the onset of WG.

the ulceration. Although the ulcers often recurred, immunosuppressive therapy was continued. As a result of this combined treatment, the activity of the underlying disease gradually decreased. C-ANCA became negative and the ESR fell to 18 mm/hr after initial treatment. The pulmonary shadow disappeared at the end of February. Furthermore, the gastric ulcers
were completely resolved by May (data not shown).

His renal function also improved, and hemodialysis was discontinued at the end of the fifth week after admission. An open renal biopsy was performed the seventh week after admission. The kidney specimen revealed fibrotic crescent-formation of approximately 70% of the glomeruli with focal global sclerosis (Fig. 8). The level of serum creatinine improved to 2.2 mg/dl. He was discharged on June 5, 1994 and is now engaged in the same office work as before admission.

DISCUSSION

Wegener's granulomatosis is characterized...
Fig. 6  Endoscopic findings (On the day of initial GI bleeding). Ethanol injection and a clip were utilized to stop the bleeding. The needle for injection is seen in this figure.

Fig. 7  Endoscopic findings (On the day of relapsed GI bleeding). Clipping was performed to stop the bleeding.
Wegener's granulomatosis with gastric bleeding

by systemic necrotizing vasculitis, granulomatous lesions of the upper and lower respiratory tract, and crescentic glomerulonephritis (1). The etiology of this disease is poorly understood, but is thought to be related to autoimmunity. Anti-neutrophil cytoplasmic antibody, especially C-ANCA (proteinase 3), has been shown to be involved in the pathogenesis of WG (2).

We encountered an interesting WG case with the rare complication of gastrointestinal bleeding. In our case, the diagnosis of WG was not too difficult because a biopsy of the nasal cavity disclosed a granuloma, and the clinical course was characteristic of WG. Proof that the gastric involvement was caused by WG was not so distinct in this case, for the histological findings in the stomach were not identified as granuloma and/or vasculitis.

We found three reports concerning WG complicated by peptic ulcers. Sakaue et al. (3) reported that a 67-year-old female patient with WG had recurrences of a giant gastric ulcer. They concluded that immunosuppressive therapy, including corticosteroids (CS) and azathioprine (AZ), improved her condition. Gastroscopic findings indicated infiltration of mononuclear cells and the presence of Langhans' giant cells in their case. Another report by Hashikata et al. (4) showed that the use of CY and CS resulted in the disappearance of multiple gastric ulcers in a male patient. In their case, the manifestations of vasculitis were not obvious, but the renal condition took a turn for the worse and the patient needed hemodialysis. Sokol et al. (5) found only two patients with gastric lesions among a total of 82 cases with WG. In the former two cases, immunosuppressive therapy given to alleviate the WG improved the gastric ulcers, although vasculitis was not demonstrated. Because immunosuppressive therapy is so effective, it appears that the immune system is involved in the pathogenesis of gastric ulcers in WG, even if vasculitis or granulomas are not observed in gastric tissues.

In contrast, Fauci et al. noted that gastrointestinal involvement was not encountered in a series of 85 patients with WG (6), while others reported several cases of WG with gastrointestinal involvement other than the stomach (5, 7–11). The lesions ranged from the esophagus to the colon, and the correlation between each disease and its specific therapy was discussed.
Kitahara et al. reported that a case of colitis with a granuloma-like lesion worsened with decreasing amounts of adrenocorticosteroids (7). According to Haworth (8), severe ileal, cecal, and rectal involvement improved rapidly after treatment with CY, AZ, and CS. Sokol (5) stated in his paper that CY therapy induced remission of inflammatory bowel disease associated with WG. He also reported that pathologic manifestations of vasculitis were often found in the GI tracts of autopsied individuals. The common point of the last three reports is that immunosuppressive therapy could improve the gastrointestinal lesions of WG, although vasculitis and granulomas in biopsied specimens were not identified.

In our patient it seems gastric ulcers were present before the onset of WG because gastritis had been pointed out in an upper GI series. He had received antibiotics and NSAIDs before admission, and then the uremia due to the RPGN might cooperate both with the initiation and with the worsening of the gastrointestinal involvement.

However, gastroendoscopic examination showed ulceration of the stomach on the fourth day of immunosuppressive therapy. The fact that ulcers in the active and healing stages were found on initial endoscopic examination also indicates that the ulcers were already present at the time of the onset of WG. Neither granulomas nor vasculitis could be demonstrated in the stomach because of the difficulty in obtaining sufficient biopsy specimens due to the serious bleeding.

Moreover, combined therapy consisting of endoscopic procedures, administration of an H2 receptor antagonist, proton pump inhibitor, and especially immunosuppressives, was found to cure the multiple gastric ulcers. The clinical evidence also suggests that gastrointestinal involvement was due to a pathologic process of WG.

In conclusion, a rare case of WG associated with repeated gastrointestinal bleeding of gastric ulcers was treated successfully with a combination of immunosuppressive therapy and routine antulcer treatment. The pathogenesis of the gastrointestinal involvement was considered a complication of WG. More attention to gastrointestinal involvement in WG is needed.

REFERENCES