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CASE REPORT

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A case of Wegener's granulomatosis associated with progressive dysphagia owing to esophageal involvement

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Abstract A 52-year-old woman was admitted to our hospital with progressive dysphagia. Upper gastrointestinal endoscopy revealed esophageal stenosis and computed tomographic scan revealed symmetrical wall thickness of the thoracic esophagus. Biopsies findings from a lesion were unremarkable. However, a definitive diagnosis of Wegener's granulomatosis was based on positive anti-neutrophil cytoplasmic antibodies directed against proteinase 3 and otorhinolaryngological manifestations. Esophageal complications are rarely reported in Wegener's granulomatosis; however, clinicians should be aware of the possibility of esophageal involvement.

Key words Anti-neutrophil cytoplasmic antibodies directed against proteinase 3 (PR3-ANCA) · Esophageal stenosis · Wegener's granulomatosis

Introduction

Wegener's granulomatosis is a systemic vasculitis and a distinct clinical and pathological disease characterized by granulomatous vasculitis of the upper and lower respiratory tracts with glomerulonephritis. Although multisystemic complications are frequent in Wegener's granulomatosis, gastrointestinal involvement is uncommon. Furthermore, esophageal involvement in Wegener's granulomatosis is rare. Thus far, only three cases of symptomatic esophageal involvement in patients with Wegener's granulomatosis have been reported.[1–3]

Here, we report a patient with Wegener's granulomatosis who experienced progressive dysphagia because of esophageal involvement. In addition, gastrointestinal involvement in Wegener's granulomatosis is discussed.

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Case report

A 52-year-old woman was admitted to our hospital on September 20, 2005 with progressive difficulty in swallowing. At the age of 20 she had a subtotal thyroidectomy for Graves' disease. In January 2005, she noticed purpura on both lower legs. In March, she had a sensation of food sticking in her throat. At the end of April, she had high fever (>39°C) for about 1 week, immediately followed by skin ulcerations of the right medial malleolus, left heel, third toe of the left foot, and the dorsum (Fig. 1). She had also been aware of loss of hearing in her left ear, gingival erosion, several oral ulcerations, and deformity of the nose. She experienced gradual progressive dysphagia and was admitted to another hospital on May 9, 2005. Upper gastrointestinal endoscopy revealed esophageal stenosis with ulcerous lesions, but showed no apparent malignant findings. In addition, findings on biopsy specimens taken from the skin ulcerations were unremarkable. On the basis of her presentation, no definitive diagnosis could be made, and she was discharged.

She presented to the department of gastroenterology in our hospital on July 4, 2005, because of increasing difficulty in swallowing. Upper gastrointestinal endoscopy demonstrated esophageal stenosis without ulcerations (Fig. 2). However, no specific findings were noted in biopsy specimens from the stenotic lesion on the esophagus. X-ray examination of the esophagus also revealed a localized stenotic lesion. She had balloon dilatation for esophageal stenosis three times, but symptoms recurred immediately.

On admission, she was 159 cm and weighed 48 kg. She had lost 6 kg during the 6 months before admission and looked unwell. Several white oral ulcerations, gingival

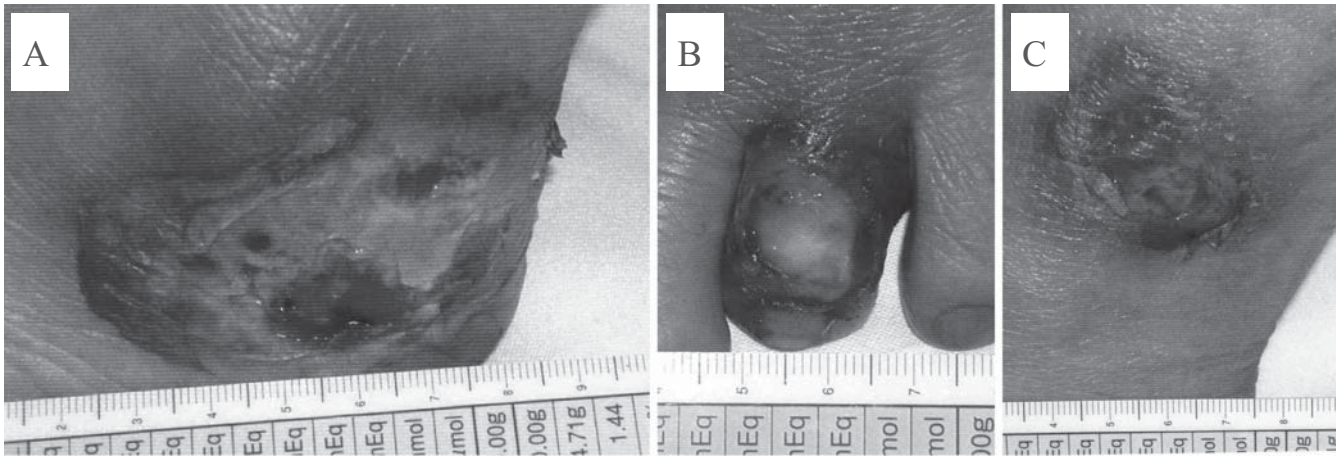

Fig. 1. Skin ulcerations of the left heel (**A**), third toe of the left foot (**B**), and the right medial malleolus (**C**)

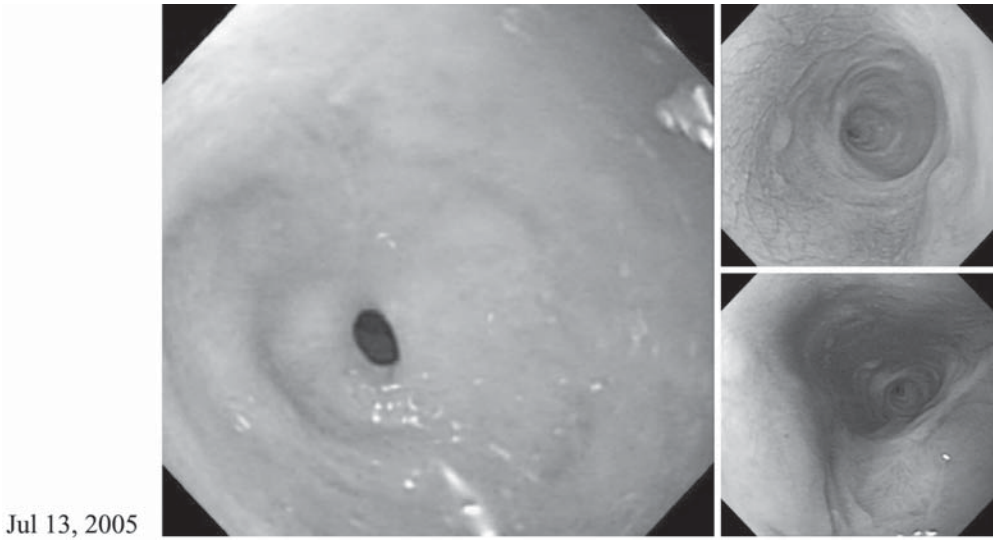

Fig. 2. Upper gastrointestinal endoscopy showing esophageal stenosis without ulcer lesions before treatment

hyperplasia (strawberry gingiva) with erosion, and a saddle nose deformity were noted. There were numerous palpable purpura and skin ulcerations on both the lower legs. A physical examination of the chest and abdomen was unremarkable. The laboratory test results showed a normal white blood cell count of $5.76 \times 10^3 \mu l^{-1}$ and a slightly high C-reactive protein level of 0.35 mg/dl. The laboratory findings revealed the presence of hypergammaglobulinemia; in particular, the immunoglobulin G level was 3580 mg/dl and the immunoglobulin A level was 582 mg/dl. Rheumatoid factor (RF) was positive at 695 IU/ml and antinuclear antibodies were positive at a titer of 1:5120, with a homogenous peripheral pattern. Furthermore, anti-neutrophil cytoplasmic antibodies (ANCA) directed against proteinase 3 (PR3) were positive at 488 U/ml. However, the test results for anti-Sm antibodies, anti-U_1RNP, anti-SS-A, anti-SS-B, and anti-topoisomerase 1 were negative. The results for ANCA directed against myeloperoxidase (MPO-ANCA) were also negative (<10 U/ml). Electrolytes, liver enzyme levels, and creatinine levels were normal. Urinary findings were also normal. The X-ray films of the chest showed no nodular cavities or infiltrates. A computed tomograpy (CT) scan of the chest revealed symmetrical wall thickness of the thoracic esophagus (Fig. 3A). These findings led us to suspect that the patient had Wegener's granulomatosis.

Figure 4 shows the clinical course of the present case following admission. Immunosuppressive therapy was initiated with a combination of prednisolone 40 mg and cyclophosphamide 50 mg daily. The oral ulcerations and purpura on the lower legs subsided completely following the treatment, and skin ulcerations gradually improved. Dysphagia also subsided immediately, and a repeat CT scan revealed complete remission of symmetrical esophageal wall thickness on day 21 following treatment (Fig. 3b). Upper gastrointestinal endoscopy also revealed no areas of narrowing and no stenotic lesions on the thoracic esophagus. The labo-

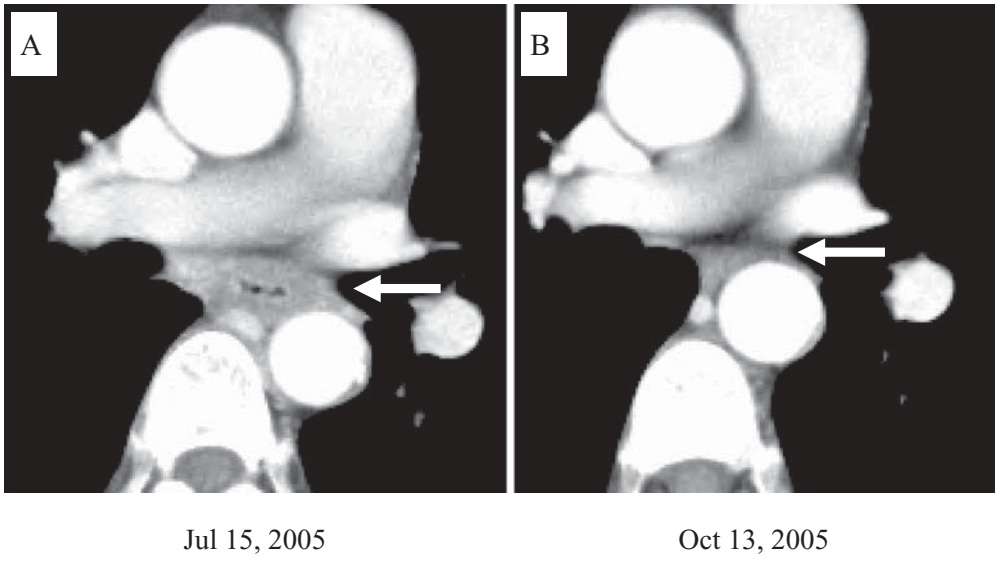

Fig. 3. Computed tomographic scan of the chest showing mural thickening of thoracic esophagus prior to treatment (**A**, *arrow*), and complete remission of thickening following treatment (**B**, *arrow*)

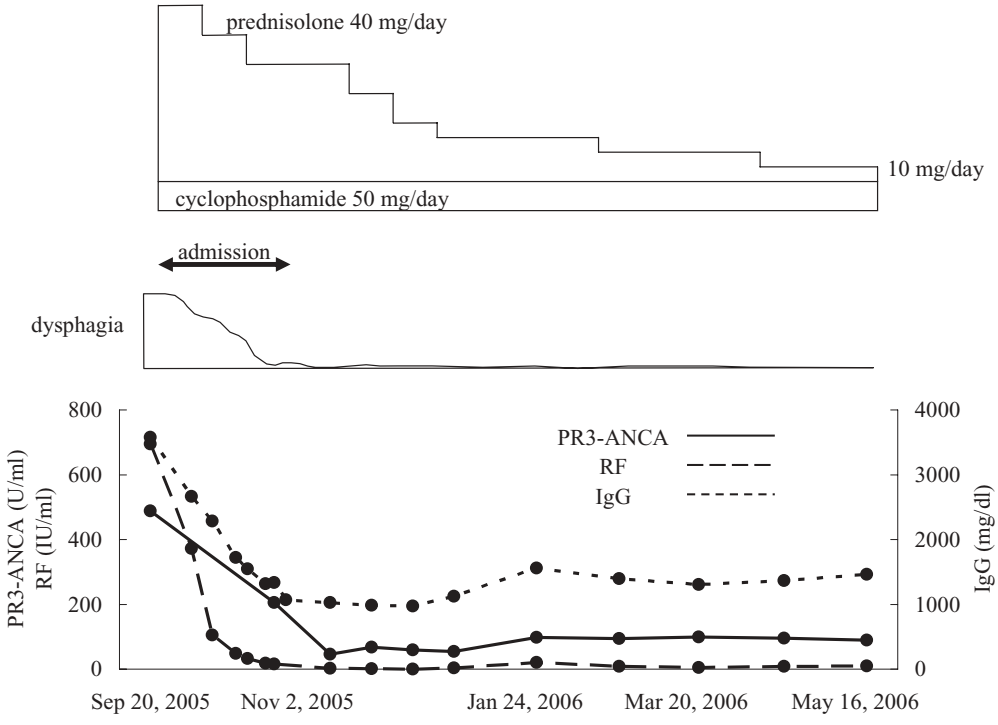

Fig. 4. Anti-neutrophil cytoplasmic antibodies directed against proteinase 3 (*PR3-ANCA*), rheumatoid factor (*RF*), and immunoglobulin G (*IgG*) levels during immunosuppressive therapy with prednisolone and cyclophosphamide

ratory results showed that immunoglobulin and RF decreased to normal levels on day 32, but antinuclear antibody levels were not measured following treatment. In addition, PR3-ANCA levels gradually decreased, although not to normal levels (205 U/ml on day 35 after treatment). During the subsequent weeks, the clinical course was progressing favorably and the PR3-ANCA level did not increase as prednisolone dosing was tapered; in addition, clinical symptoms mostly disappeared. She was discharged on November 2, 2005. In December 2006, she was treated with prednisolone 10 mg/day and cyclophosphamide 50 mg/day. From that time she has had no relapse of symptoms associated with Wegener's granulomatosis.

Discussion

Gastrointestinal symptoms associated with Wegener's granulomatosis are uncommon. Autopsy studies of patients with Wegener's granulomatosis showed gastrointestinal involvement in 24% of cases, although none of these patients had symptoms associated with gastrointestinal involvement.[4] A large prospective study of 158 patients with Wegener's granulomatosis reported no gastrointestinal involvement throughout the course of disease,[5] and only scattered cases of gastrointestinal involvement associated with Wegener's granulomatosis have been reported.[6–8]

Furthermore, esophageal involvement has rarely been reported in Wegener's granulomatosis. Certainly, esophageal symptoms that are attributed to reflux esophagitis or infectious complications have been reported in Wegener's granulomatosis. However, in autopsy case studies of 29 patients, only 1 patient had asymptomatic esophageal arteritis.[9] Symptomatic esophageal involvement associated with Wegener's granulomatosis itself has been reported in one case of odynophagia owing to erosive gastritis,[1] in a second case of odynophagia owing to vasculitic ulcerations of the esophagus,[2] and in a third case of retrosternal pain owing to esophageal and gastric ulcers.[3] In addition, a case of dysphagia owing to oropharyngeal involvement in a patient with Wegener's granulomatosis has been reported.[10] However, there are no prior cases of dysphagia owing to esophageal involvement in patients with Wegener's granulomatosis.

The reason for the uncommon gastrointestinal involvement in Wegener's granulomatosis is not well understood. PR3-ANCA possibly plays a primary role in the pathogenesis of Wegener's granulomatosis.[11,12] A different immunological reaction induced by PR3-ANCA in the gastrointestinal tract compared with other areas, such as the upper and lower respiratory tracts, may help explain the lack of gastrointestinal symptoms with Wegener's granulomatosis. On the other hand, it has been suggested that gastrointestinal manifestations appear in the early stages of the disease,[13] or that esophageal involvement may be a marker of disease severity.[1] Additional studies are required to reach a conclusion on this issue.

The diagnosis of Wegener's granulomatosis requires histopathological evidence as well as laboratory or physical evidence. To establish a diagnosis of Wegener's granulomatosis, there should be clinical evidence of disease in two or three principal sites with histopathological confirmation in at least one, and preferably two sites.[14] In the present case, unfortunately, biopsy specimens taken from the stenotic lesion on the esophagus or skin ulcerations showed no evidence of specific manifestations that would have lead to the distinct histopathological diagnosis of Wegener's granulomatosis. Although it is speculated that pulmonary tissue offers the highest diagnostic yield in Wegener's granulomatosis, the findings in both lung fields on the X-ray films and CT scan of the chest were unremarkable in the present case. Furthermore, it was suggested that endoscopic biopsies were too superficial to obtain histological proof of gastrointestinal complications.[8,15]

We diagnosed this patient with Wegener's granulomatosis on the basis of clinical findings without histopathological confirmation for the following reasons. First, it has been reported that the specificity of a positive PR3-ANCA titer for Wegener's granulomatosis is high, and the presence of PR3-ANCA is extremely helpful in differentiating Wegener's granulomatosis from other diseases.[11,16] Second, although a definite diagnosis of Wegener's granulomatosis generally cannot be made before active generalized symptoms develop, hearing loss, deformity of the nose (a saddle nose), and gingival hyperplasia (strawberry gingiva) are characteristic in the early stages of this disorder.[17–19] Patients with relapsing polychondritis may have a saddle nose that can be distinguished from that seen with Wegener's granulomatosis by the presence or absence of auricular involvement.

Establishing a diagnosis of Wegener's granulomatosis can be difficult, especially in the early stages of the disease or in limited forms of the illness, during which pulmonary and renal involvement do not occur. In addition, the diagnosis is often made clinically, because biopsy specimens taken from the lesions frequently show no evidence of specific manifestations; it is also not uncommon to require repeated biopsies spanning many months for histopathological confirmation. It is suggested that progression of Wegener's granulomatosis is universally rapid and fatal, usually within a few months after the onset of clinically apparent renal disease. To manage Wegener's granulomatosis effectively, clinicians must establish the diagnosis of the disease without delay, and recognize variability in the clinical course and severity of the disease. Therefore, it is speculated that the detection of PR3-ANCA and initial otorhinolaryngological manifestations may be valuable for the early diagnosis of Wegener's granulomatosis.

Causes of esophageal ulcerations include acid reflux, infection (fungal or tuberculosis), and others. In the present case, reflux esophagitis was unlikely because esophageal ulcerations subsided spontaneously without antacids, oral proton pump inhibitors, or H_2 receptor antagonists. Immunosuppressive therapy relieved her clinical symptoms, including symmetrical esophageal wall thickness, suggesting that the cause of esophageal ulcerations was esophageal involvement of Wegener's granulomatosis itself. Thus, it is unlikely that the cause of the esophageal ulcer was infection. Biopsy specimens from the esophageal stenotic lesion also revealed no evidence of infectious disease. This present case indicates that esophageal involvement might be considered in the natural history of Wegener's granulomatosis.

The histopathological manifestations of Wegener's granulomatosis are characterized by necrotizing vasculitis of small vessels with granulomatous formation. In patients with Wegener's granulomatosis, therefore, it is speculated that esophageal stenosis would be attributed to ischemic changes in the esophageal wall owing to vasculitis and changes in wall thickness because of infiltration of inflammatory cells and granulomatous formation itself.

In summary, we reported a patient with Wegener's granulomatosis who experienced progressive dysphagia because of esophageal involvement. Treatment with prednisolone and cyclophosphamide resulted in complete remission of the disease. Clinicians should be aware of the existence of primary esophageal involvement associated with Wegener's granulomatosis.

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