CASE REPORT

Wegener’s Granulomatosi s Complicated by Intestinal Ulcer due to Cytomegalovirus Infection and by Thrombotic Thrombocytopenic Purpura

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Abstract

A 61-year-old woman was admitted to our hospital because of acute kidney injury. She complained of general fatigue, appetite loss, and a high fever. Nodular lesions were observed on chest X-rays and there were >100 erythrocytes per high power field in her urinary sediment. A renal biopsy revealed necrotizing granulomatous glomerulonephritis, and her serum proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) titer was elevated (55 EU). Based on these findings we made a diagnosis of Wegener’s granulomatosis (WG). Hemodialysis was started immediately after admission. Steroid therapy was administered and her symptoms were relieved, but her renal function did not improve. On the 50th hospital day her condition suddenly became complicated by hemoperitoneum and massive intestinal bleeding, and the descending, transverse, ascending colon and part of the ileum were surgically resected. The cytomegalovirus (CMV) antigen titer was elevated, and histologic examination of the bowel specimen showed positive staining for CMV in the ulcer lesion, suggesting that CMV infection had caused the bowel hemorrhage. After treatment with ganciclovir, the bleeding was resolved and the CMV antigens became negative. We considered that this patient was further complicated by thrombotic thrombocytopenic purpura (TTP) because of thrombocytopenia, hemolytic anemia and neurologic symptoms. She was treated by plasma exchange. We report here a case of WG complicated by acute intestinal ulcer due to CMV infection and by TTP.

Key words: Wegener’s granulomatosis, intestinal ulcer, cytomegalovirus infection, thrombotic thrombocytopenic purpura, progressive glomerulonephritis, plasma exchange

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Introduction

Wegener’s granulomatosis (WG) is a systemic disease of unknown etiology characterized by necrotizing vasculitis and granulomatous inflammation. It typically involves the upper airways, the lungs and kidneys, although the inflammatory destructive lesions may develop in almost any organ. Some patients with WG are at risk for opportunistic infections because they are immunocompromised by both the underlying disease process and the drugs used to treat it. As far as we know, the intestinal involvement and thrombotic thrombocytopenic purpura (TTP) in WG are infrequently reported. Here, we report a rare case of WG with severe intestinal involvement due to cytomegalovirus (CMV) infection which was complicated by TTP.

Case Report

A 61-year-old Japanese woman was admitted to her local hospital because of general fatigue at the end of February and presented with a two-week history of common cold

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symptoms. She had no family history of renal disease. She did not consume alcoholic beverages but had smoked 10-20 cigarettes a day for 40 years. Laboratory tests revealed a markedly elevated C-reactive protein (CRP) value (11.18 mg/dl), an elevated serum creatinine level (2.58 mg/dl), proteinuria (2+), hematuria (3+, >100/high power field), and a urinary sediment leukocyte count of >100/high power field. Urinary tract infection was diagnosed and treated with Cefmetazole sodium (1 g/day) intravenously, but her CRP value remained unchanged, and her serum creatinine value remained elevated. At the beginning of March, she was transferred to our hospital for acute kidney injury. On admission, she complained of general fatigue and appetite loss. Her body height was 160 cm, and she weighed 65.7 kg. The patient had a fever of 38.0°C, her blood pressure was 133/74 mmHg, and her pulse rate was 100/min. She was alert, but her eyelids were edematous. Auscultation of her chest revealed normal vesicular sounds, but she had a systolic murmur. Her abdomen was soft and non-tender. Purpura was found on both feet. There were no significant neurological findings. The laboratory data on admission are shown in Table 1. Proteinuria (2+) and hematuria (3+) were present. The white blood cell count was elevated to 23,070/μl. The serum creatinine level was elevated to 7.62 mg/dl, and the CRP level was 15.62 mg/dl. The proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) titer was 55 EU (SRL, Inc., Tokyo). Chest X-rays and a computed tomography (CT) scan of the chest revealed two nodules, one that was 1 cm in diameter and located in the right lower lobe and pleura, and the other was 2 cm in diameter and located in the right middle lobe (Fig. 1). There were no abnormal findings in the abdominal X-ray or electrocardiogram. Ultrasonography revealed enlarged kidneys.

The patient’s clinical course is shown in Fig. 2. Hemodialysis was started immediately for the acute kidney injury. Regular hemodialysis (3 times a week) was required. A needle biopsy was performed to diagnose the kidney disease. Of the 11 glomeruli obtained, 3 showed global sclerosis. Cellular crescents were observed in 8 glomeruli (Fig. 3a). Necrotizing granulomatous glomeruli with dissolution of Bowman’s capsule were seen (Fig. 3b, c). Massive CD68 positive cell infiltration was detected in the granulomatous lesions (Fig. 3c, d). Renal interstitium showed moderate fibrosis and inflammatory cell infiltration. Tubular atrophy and necrosis of tubular epithelial cells were also seen. There were no signs of vasculitis at the levels of the arteriole and interlobular artery. We made a diagnosis of granulomatous and necrotizing crescentic glomerulonephritis with moderate tubulointerstitial injury. A skin biopsy showed no evidence of vasculitis. A CT-guided lung biopsy failed to yield a specimen from the center of a nodular lesion, but the lung specimen showed lymphocyte infiltration and inflammatory cells.

According to the criteria proposed by the American College of Rheumatology [1990 criteria for the classification of WG] (1) we made a diagnosis of WG based on the following evidence: abnormal chest radiograph with nodular lesions, a urinary sediment abnormality (>100 erythrocytes per high power field), necrotizing granulomatous glomerulonephritis, and a high serum PR3-ANCA titer (55EU). The Birmingham Vasculitis Activity Score (BVAS) was 18 points (General 2, Cutaneous 2, Chest/Pulmonary 2, Renal 12). The patient was treated with a steroid (prednisolone, PSL) 60 mg/day (1 mg/kg/day) intravenously from day 8, and her condition, including her high fever and general fatigue, improved. Her temperature immediately returned to within the normal range. The serum CRP and PR3-ANCA values remain elevated despite the CRP level remained unchanged.
gradually decreased after the start of PSL.

On day 50, the patient suddenly developed stomachache and went into shock. Her hemoglobin level had fallen to 4.4 g/dl, and she was transfused 50 units of packed red cells. Immediate angiography demonstrated active bleeding from the superior pancreaticoduodenal artery, branch of the gastroduodenal artery (Fig. 4). The bleeding was treated by embolism with a tornade coil, and 4500 ml of blood was drained from the abdominal cavity. On day 58, she again developed abdominal pain, and it was associated with massive hematochezia. Colonoscopy revealed coagulated blood in the colon and terminal ileum, but no clear bleeding source. Red blood cell scintigraphy and angiography did not indicate any source of bleeding either. From day 60 onward
the patient was transfused with 10 units of packed red cells daily. She was also given pulses of intravenous methylprednisolone, because the bleeding was thought to be associated with the WG process. Because of persistent hematochezia, the descending, transverse, ascending colon, and part of the ileum were excised on day 66, and an artificial anus was created. Histological examination of the resected colon revealed ulcers. Immunohistochemical staining for CMV revealed the CMV near the ulcer lesion (Fig. 5), and we assumed that CMV infection had caused the bowel hemorrhage. Since the CMV antigen titer was elevated on day 63, the patient was treated with ganciclovir. After treatment with ganciclovir, the hematochezia resolved, and CMV antigen assays on day 81 were negative.

On day 74, we treated the patient with micafungin sodium (50 mg/day, every day), because the serum 1→3-β-D-glucan value had increased to 190.9 pg/ml, indicating a mycosis infection. After taking the medication, the patient developed depression and excitement. Her platelet count and hemoglobin gradually decreased to $2.1 \times 10^4/\mu l$ and 7.8 g/dl, respectively. Schistocytes were observed in her blood, and the total-bilirubin value was elevated to 3.0 mg/dl. Lactate dehydrogenase was also elevated to 770 U/l, and haptoglobin was <10 mg/dl. Based on these findings a diagnosis of TTP was made. Coagulation factor values, including the prothrombin time, activated partial thromboplastin time, and fibrinogen values were within the normal range, ruling out disseminated intravascular coagulation. Plasma exchange with 40 units of fresh frozen plasma was performed 8 times between day 82 and day 100. We suspected that the micafungin sodium had caused the TTP, and thus discontinued it on day 90. The TTP was improved with each plasma exchange.

On day 112, the patient’s temperature rose to 38.0°C, and
a ventral hernia was diagnosed. Her leukocyte count was 23,000/μl, and an abdominal CT scan indicated an abscess or ascites in the abdominal cavity. A chest CT scan revealed a newly formed hollow lesion in the upper left lung, despite shrinkage of the nodule in the right lower lobe and pleura and in the nodule in the right middle lobe (Fig. 6). The differential cause of the new lung lesion was pulmonary bacteria, pulmonary tuberculosis, pulmonary mycosis, lung cancer, and WG. Serum PR3-ANCA and tumor markers were negative. The patient was treated with an intravenous antibiotic (Ceftazidime). She complained of abdominal pain, and her ventral hernia had ruptured on day 124. Pseudomonas aeruginosa was detected in a bacterial culture of pus from the ruptured hernia. Antibiotic therapy was continued and abdominal drainage was performed. The inflammatory reaction, abdominal damage, and the hollow lesion in the chest CT improved. On day 153, a bacterial culture was negative, and the antibiotic was discontinued. PSL was gradually reduced to 20/30 mg orally every other day, and the patient was discharged on day 176.

**Discussion**

WG is characterized by necrotizing granulomatous vasculitis involving the respiratory tract, kidneys and other organs. Serum PR3-ANCA is frequently elevated in patients with WG (2-4). Unusual manifestations of intestinal involvement in WG have been reported (5). Storesund et al reported six cases of severe intestinal involvement in WG. They stated that intestinal perforation and necrosis should be regarded as complications of WG itself rather than as conditions induced by medical therapy (6). On the other hand, bowel hemorrhage due to CMV has been reported in patients with WG on immunosuppressive therapy. CMV-related disease is a relatively frequent complication of immunosuppressive treatment for systemic vasculitis, such as WG (7, 8). The bowel specimen in the present case stained positive for CMV in the ulcer lesion. We therefore concluded that the CMV infection had caused the bowel hemorrhage.

Intraperitoneal hemorrhage can occur in a variety of conditions. Ovarian hemorrhage and rupture of a tumor or aneurysm are common causes. In this patient, the superior pancreaticoduodenal artery, a branch of the gastroduodenal artery, ruptured. Some cases of WG complicated by the rupture of medium or large vessels with aneurysm formation have been reported previously (9-11). The present patient might have had vasculitis as a result of WG, which in turn may have led to the intraperitoneal hemorrhage—even though an aneurysm was not detected. Based on the findings in the bowel specimen, the patient might have had CMV vasculitis. The cause of the ruptured artery in the present patient was not clear.

Our patient’s symptoms mimicked an exacerbation of her underlying vasculitis; they were resolved in response to antiviral therapy. Since both WG and CMV infection can cause diffuse pulmonary infiltrates, glomerulonephritis, and systemic vasculitis, it is difficult to differentiate between WG and CMV infection, as in our case.

The spectrum of infectious complications in immunocompromised WG patients usually involves bacterial or fungal pathogens (12). Bacterial infections, especially of the nasal sinuses and respiratory tract, can be confused with exacerbations of the underlying illness (13). Our patient was treated with prednisone and had a Pseudomonas aeruginosa infection, mycotic infection, and CMV infection. Infections are one of the most important prognostic factors of WG. To avoid potential harmful consequences of inappropriate use of immunosuppressive therapy, we suggest early examination for CMV antigens and (1→3)-β-D-glucan, and bacterial cultures.

We considered that this patient was complicated by TTP because of thrombocytopenia, hemolytic anemia and neurologic symptoms. The cause of TTP can be varied; pregnancy, collagen disease, infection, malignancy, cancer chemotherapy, oral contraceptive pill use, and familial heredity are known to cause TTP. The cause of TTP in this patient was not clear. We could not rule out the possibility that the administration of micafungin sodium had caused the TTP, so its use was stopped. The CMV infection and WG might also have been related to the etiology of TTP in this patient. Endothelial damage as a result of WG, CMV infection and drug use may have promoted the development of TTP in this patient. Several reports have described TTP as a compli-
cation of certain forms of rheumatic disease, including systemic lupus erythematosus and systemic sclerosis (14, 15), but to our knowledge there has been only one report of WG complicated by TTP (16).

Conventional treatment for TTP, including plasma exchange, was effective in our patient, just as in the patient in the report of Rock et al (17). We emphasize the need to consider TTP in the differential diagnosis when thrombocytopenia develops in a patient with vascular disease. Early, proper treatment of TTP can reduce morbidity and mortality in such patients.

Taken together, we report a case of WG complicated by necrotizing granulomatous glomerulonephritis, and pulmonary nodules that were also complicated by uncommon diseases including Pseudomonas aeruginosa infection, mycosis, CMV infection, and TTP.

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References