Clostridium difficile Infection Induced by Pregabalin-associated Agranulocytosis

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Abstract

A 33-year-old man who had recently undergone surgery for cervical spondylotic myelopathy was prescribed pregabalin for neuralgia, and the dose was increased to 600 mg/day during hospitalization. However, the patient was diagnosed with a *Clostridium difficile* infection on day 34 after admission. A complete blood count showed agranulocytosis (neutrophil count: 105/ μ L). We did not observe any changes in vital signs, a relative increase in band cells, or intestinal edema. The patient's agranulocytosis resolved after withdrawing pregabalin. This is the first reported case of agranulocytosis associated with pregabalin. Periodic monitoring of the white blood cell count is therefore considered to be useful in patients receiving high-dose pregabalin therapy.

Key words: *Clostridium difficile*, pregabalin, agranulocytosis, neutropenia

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Introduction

Agranulocytosis [defined as a white blood cell (WBC) count of $<500/\mu$ L] is a rare but important medical emergency. The condition is drug-induced in more than 70% of cases (1, 2) and can facilitate the development of life-threatening bacterial infections due to a lack of appropriate immunity (3). Several drugs have been reported to be causative agents of agranulocytosis. For example, antithyroid drugs, are considered to be particularly high-risk agents, followed by dipyrrone, trimethoprim/sulfamethoxazole, and carbamazepine (4). The literature is sparse regarding the association between neutropenia and gamma-aminobutyric acid (GABA) analogs (5, 6); all reported patients were asymptomatic, and the incidence of bacterial infection has not been reported.

We herein describe a case of *Clostridium difficile* infection (CDI) induced by pregabalin-associated agranulocytosis.

Case Report

A 33-year-old man who had been hospitalized in our neurosurgery department for cervical spondylotic myelopathy complained of fever and diarrhea 32 days after admission. His medical history included a facial injury sustained by a chopstick eight years previously, and he had experienced multiple surgical site infections that required the frequent use of antimicrobial agents one year after the injury. The surgical site infection had not recurred within the last seven years, and there was no previous history of CDI. The patient had no history of allergies, renal impairment, or hematological disorders. He had been prescribed quazepam, olopatadine, diclofenac, and omeprazole by his family physician for worsening numbness, neuropathic pain, and muscle weakness in the left arm, along with a sleep disturbance caused by spondylotic myelopathy for more than three months. The initial evaluation performed at admission revealed no remarkable laboratory findings, with a normal WBC count (7,300/ μ L) and a creatinine level of 0.73 mg/dL [estimated creatinine clearance (Cockcroft-Gault formula): 145 mL/

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Figure 1. Clinical course of the present patient, a 33-year-old man with cervical spondylotic myelopathy who was prescribed pregabalin for neuropathic pain.

Figure 2. Results of a microscopic stool examination performed on day 34. The arrowheads indicate WBCs in the stool.

min].

Before the onset of fever and diarrhea, the patient underwent C5/C6 foraminotomy on day 13. Ceftriaxone was administered until day 27 to prevent surgical site infection. Pregabalin was prescribed two days postoperatively for neuropathic pain at a dose of 150 mg/day (day 16); this dose was increased to 600 mg/day over the next two weeks. The WBC count on day 29 was unremarkable (5,700/ μ L).

A spike in fever and watery diarrhea developed on day 32, and the patient was evaluated by our infectious diseases department on day 34 due to his low WBC count and high C-reactive protein level. The assessment showed the patient to be well oriented without neck stiffness. His vital signs were as follows: body temperature, 39.9°C; blood pressure,

150/86 mmHg; pulse rate, 112/min; respiratory rate, 28/min; and percutaneous oxygen saturation on room air, 94%. He had no pulmonary rales, skin rashes, lymphadenopathy, or joint swelling, and no exudate or rashes were noted at the surgical site. Mild tenderness was observed in the left abdominal region. The laboratory findings showed a low WBC count (1,500/ μ L) with agranulocytosis (neutrophil count: 105/ μ L) and a high C-reactive protein level (27.0 mg/dL) (Fig. 1). A direct microscopic examination of a blood film revealed neither myelocytes nor metamyelocytes, and the proportion of band neutrophils was 4% on the peripheral blood sample. No anemia, thrombocytopenia, renal insufficiency, or coagulopathy were present. Two blood cultures showed no signs of bacteria, while abdominal computed tomography demonstrated no evidence of infection.

Pregabalin was discontinued the same day, and treatment with filgrastim and oral vancomycin was started after the patient exhibited a positive *C. difficile* toxin assay result (*C. DIFF QUIK CHEK COMPLETE*, Alere Medical Co., Ltd., Tokyo, Japan) and a positive WBC count in a stool specimen (Fig. 2). Omeprazole was simultaneously discontinued, but quazepam, olopatadine, and diclofenac were continued. The patient's agranulocytosis promptly improved, and the patient was discharged on day 41. Vancomycin was prescribed for 12 days, and the diarrhea did not reoccur. Treatment with omeprazole was restarted after discharge. No recurrence of neutropenia was detected at the follow-up visit one month later.

Discussion

In this case, agranulocytosis was observed approximately two weeks after the initiation of pregabalin therapy, and it promptly resolved following the discontinuation of this medication. Although the patient received other drugs during hospitalization, these agents had all been prescribed for several months prior to admission, and he continued to take all drugs during and after the episode of agranulocytosis. Treatment with omeprazole was terminated with pregabalin after the onset of agranulocytosis; however, omeprazole did not induce neutropenia when therapy was reinitiated during outpatient management. Based on the patient's prescription drug history, we considered pregabalin to be the only drug associated with the development of agranulocytosis.

CDI was diagnosed in addition to agranulocytosis based on the patient's clinical symptoms and a positive toxin assay result obtained on day 34. The preceding use of antimicrobial agents and/or proton pump inhibitors is known to be a major risk factor for CDI (7-9), and the present patient had taken both of these medications. Neutropenia is also considered to be a risk factor for a CDI (10), and the development of CDI in the present patient was consistent with the occurrence of neutropenia. These findings suggest that the patient's agranulocytosis had likely triggered CDI due to the use of proton pump inhibitors and a disturbance in the patient's normal intestinal flora following treatment with antimicrobial agents.

Bacteria are the etiological agents of agranulocytosis, and it has been reported that bacterial infections can cause transient neutropenia. In cases of bacteria-induced agranulocytosis, a rapidly deteriorating condition is usually accompanied by changes in vital signs or a relative increase in band cells, neither of which were observed in the present case. Furthermore, the patient exhibited no edematous intestinal changes suggestive of a severe CDI (11). Therefore, we propose that the patient's neutropenia was induced by pregabalin therapy, although we did not confirm the presence of neutropenia prior to the onset of diarrhea. We believe that CDI may be associated with a decreased neutrophil count.

Pregabalin is a lipophilic GABA analog (12) that was first introduced into the market in 2005. It has greater analgesic potency than gabapentin (13), and its efficacy in the treatment of neuralgia has been well described (14). Recent studies have also demonstrated the efficacy of this drug in the treatment of fibromyalgia (15), epilepsy (16), and general anxiety disorder (17). Pregabalin is usually well tolerated; however, adverse effects can include dizziness, somnolence, peripheral edema, asthenia, dry mouth, and weight gain (18). There have also been reports of heart failure (19), rashes (20), and increased liver enzyme levels (21). Neutropenia has rarely been reported as an adverse effect of pregabalin, with only a single case report of pregabalin-associated neutropenia (5). In that patient, mild neutropenia (1,262/ μ L) occurred two days after the administration of

pregabalin (75 mg/day) and rapidly resolved when the dose of pregabalin was discontinued. In that case, a direct toxic effect on bone marrow was considered to constitute the mechanism of action of pregabalin with respect to the development of neutropenia. However, the neutropenia described in that report was not as severe as that noted in the present case. To the best of our knowledge, this is the first case of pregabalin-associated agranulocytosis.

We considered a number of factors that may have been involved in the onset of pregabalin-associated agranulocytosis in this case. For example, pregabalin was prescribed at the maximum recommended dose of 600 mg/day. In a previous study of pregabalin therapy, Arroyo et al. reported that adverse effects, such as somnolence, dizziness, ataxia, and tremors, were more frequent among patients who received a dose of 600 mg/day than in those who received 150 mg/day (22). Kamel et al. also reported that the adverse effect of constipation induced by pregabalin is dose-dependent and more severe among patients treated with higher doses of pregabalin (23). The results of these investigations imply that neutropenia is more frequent and severe in patients taking high doses of pregabalin, possibly explaining the difference in neutropenia severity between the previously described case and the current patient.

We were unable to monitor the serum concentration of pregabalin in this patient, which is a limitation of this case report. In addition, we did not perform a bone marrow analysis or serum antibody screening to investigate other etiologies of agranulocytosis, such as hematological disorders, collagen diseases, or viral infections (4). However, we believe that these conditions are unlikely causes of hospital-onset agranulocytosis because they can be differentiated based on clinical characteristics.

In conclusion, we described a case of CDI complicated by agranulocytosis that occurred when the pregabalin dose was increased. Periodic WBC count monitoring is required in patients receiving high-dose pregabalin therapy.

The authors state that they have no Conflict of Interest (COI).

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