INTERNAL MEDICINE

□ CASE REPORT □

Giant Cell Arteritis which Developed after the Administration of Granulocyte-colony Stimulating Factor for Cyclic Neutropenia

Masataka Umeda[1], Jin Ikenaga[1], Tomohiro Koga[1], Toru Michitsuji[1], Toshimasa Shimizu[1], Shoichi Fukui[1], Ayako Nishino[1], Yoshikazu Nakasima[1], Sin-ya Kawashiri[1], Naoki Iwamoto[1], Kunihiro Ichinose[1], Yasuko Hirai[1], Mami Tamai[1], Hideki Nakamura[1], Tomoki Origuchi[2] and Atsushi Kawakami[1]

Abstract

A 78-year-old woman diagnosed with cyclic neutropenia 5 years previously had been treated with recombinant granulocyte-colony stimulating factor (G-CSF). She developed fever, tenderness and distension of temporal arteries after the treatment with G-CSF. Magnetic resonance imaging and ultrasonography revealed wall thickening of the temporal arteries. She was therefore diagnosed with giant cell arteritis (GCA). Small vessel vasculitis has been reported as a complication of G-CSF. However, the development of large vessel vasculitis after G-CSF treatment is quite rare. To our knowledge, the present case is the first report of GCA suspected to be associated with coexisting cyclic neutropenia and G-CSF treatment.

Key words: cyclic neutropenia, giant cell arteritis, granulocyte-colony stimulating factor, vasculitis

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Introduction

Giant cell arteritis (GCA) is a type of vasculitis that occurs among elderly patients. GCA mainly affects large and medium-sized vessel such as the aorta and external carotid arteries and their branches. The activation of dendritic cells (DC) caused by microorganisms has been suggested to play a role in the pathogenesis of GCA (1). T helper 1 (Th1)-inducing signals and interleukin 17 (IL-17) have also been reported to be involved in this condition (2). However, the precise mechanism remains poorly understood. We herein describe the first known patient with GCA that developed while using granulocyte-colony stimulating factor (G-CSF) for the treatment of cyclic neutropenia.

Case Report

A 78-year-old woman who was suffering from cyclic neutropenia had been treated with filgrastim, a recombinant G-CSF for five years. The frequency of neutropenia was once every two months. After each onset of neutropenia, she had been treated with filgrastim 500 mg three times. One month before being admitted, she developed fever, malaise, headache in the temples, jaw claudication, visual abnormality, and double vision after the administration of filgrastim. On admission, her body temperature was 37.7℃. Her blood pressure, pulse rate, and respiratory rate were normal. Physical examination revealed tenderness and distension of the temporal arteries and double vision when gazing to the right. No difference in her blood pressure between arms and vascular bruit in the chest were observed. The initial laboratory studies revealed the following: white blood cell count

[1]Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Japan and [2]Department of Rehabilitation Sciences, Nagasaki University Graduate School of Biomedical Sciences, Japan
Received for publication October 17, 2015; Accepted for publication November 23, 2015
Correspondence to Dr. Masataka Umeda, masataka_0807@yahoo.co.jp

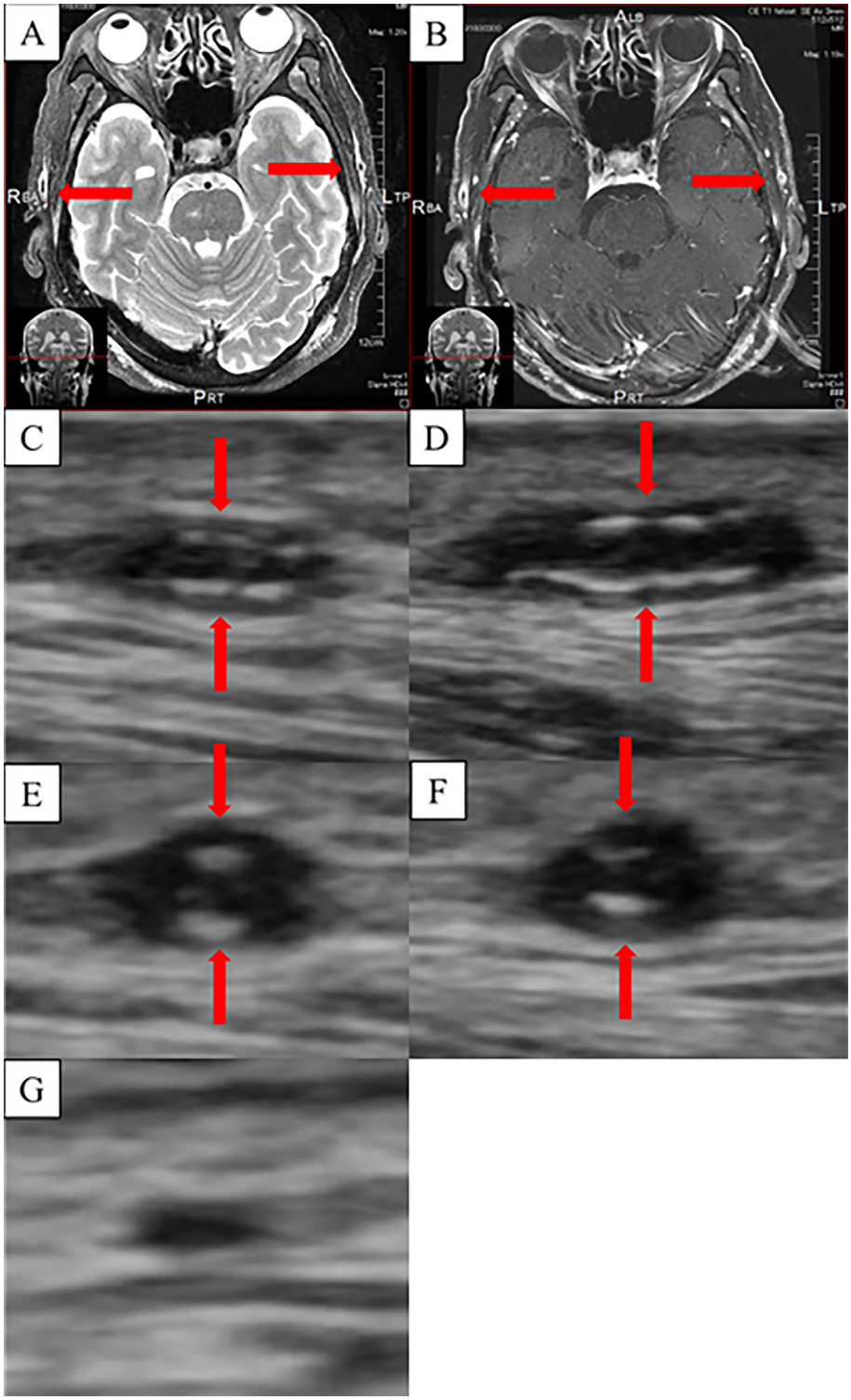

Figure. **Magnetic resonance imaging of the temporal arteries (A: fat suppression T2-weighted image. B: fat suppression and contrast-enhanced T1-weighted image) showed arterial wall thickness and abnormal contrast enhancement (indicated by arrows). Ultrasonography (C: right, longitudinal. D: left, longitudinal. E: right transverse. F: left transverse) of the temporal arteries revealed hypoechoic halo (halo sign). The arrows indicate the sites of inflammation. The halo sign improved after treatment (G: right transverse).**

of 7,200/μL (75.0% neutrophils, 12% lymphocytes), hemoglobin of 12.8 g/dL, platelet count of 378,000/μL, and C-reactive protein (CRP) of 14.28 mg/dL. The aspartate aminotransferase (AST) was 20 IU/L, alanine aminotransferase (ALT) was 17 IU/L, lactate dehydrogenase was 133 IU/L, and creatine phosphokinase was 15 IU/L. Rheumatoid factor, anti-nuclear antibodies (ANA), anti-DNA antibodies, anti-ribonucleoprotein (RNP) antibodies, anti-SS-A antibod-

Table. A Cytokine Multiplex Array of the Patient's Serum from the Present Case at the Time of Admission. The 95% Confidence Interval of the Serum Cytokine Level from Healthy Individuals (n=38) is Indicated as a Control (Units Pg/mL).

	present case	HC (95% CI)		present case	HC (95% CI)
G-CSF	16.5	27.1-39.5	IL-1β	Undetectable	1.33-4.32
GM-CSF	8.8	20.6-60.9	IL-6	44.8	0.72-7.74
GRO	1,341.9	732.2-921.3	IFN-α	9.65	36.1-72.5
IFN-γ	13.9	18.5-44.2	IP-10	502.9	232.1-336
IL-12 p40	Undetectable	11.9-36.1	TNF-α	15.9	7.91-12.1
IL-12 p70	3.24	6.76-50.7	VEGF	1,116.0	200.2-409.2
IL-17	2.86	7.20-20.4	IL-18	92.3	58.1-102.4

ies, myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), and proteinase 3 ANCA were all negative. The viral markers for hepatitis B, hepatitis C, and human T lymphocyte virus-1 were all negative. The procalcitonin concentration was 0.069 ng/mL. The β-D glucan concentration was 19.5 pg/mL. The interferon γ (IFN-γ) release assay (T spot®) and two sets of blood cultures were negative. She had *HLA-DRB1*04* alleles. The chest X-ray and thoracoabdominal computed tomography (CT) findings did not show any cause of inflammation. Magnetic resonance imaging of the temporal arteries (Figure A, B) showed arterial wall thickness and abnormal contrast enhancement. Ultrasonography (Figure C-F) revealed a hypoechoic halo (halo sign) around the temporal arteries. The funduscopic findings were normal. No other large vessel vasculitis was found by head magnetic resonance angiography and thoracoabdominal CT. She was diagnosed with GCA based on these findings. We could not perform a temporal artery biopsy because an immediate initiation of therapy was required to treat her visual disturbance. The induction of prednisolone at 40 mg/day resulted in a rapid improvement of her symptoms and inflammation. The halo sign observed on ultrasonography also improved (Figure G). Based on the fact that the neutrophil counts elevated after the initiation of prednisolone therapy, we eventually concluded that the cause of cyclic neutropenia had most likely been autoimmune neutropenia. Tapering of the dosage of prednisolone has been continuing.

We performed a cytokine multiplex array of the patient's serum in the present case at the time of admission (Table). The 95% confidence interval of each serum cytokine level was calculated from healthy individuals (n=38) as a control. We found that tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6) and vascular endothelial growth factor receptor (VEGF) to have all increased, whereas IL-12, IL-17, and IFN-γ were not elevated.

Discussion

To the best of our knowledge, this is the first report that GCA developed during the use of G-CSF. Some form of vasculitis occurred in 4.1% of patients with severe chronic neutropenia who received G-CSF treatment. The involved site was the skin in almost all cases and more than 50% of these cases were proven to be leukocytoclastic vasculitis by biopsy (3). The vasculitis caused by G-CSF usually develops after the initial treatment, but there is also a report showing such dermatitis to develop after multiple administrations of G-CSF (4). The development of large vessel vasculitis including GCA or Takayasu's arteritis after G-CSF treatment is quite rare. To our knowledge, only two cases have been previously reported to have large vessel vasculitis. Darie et al. reported a 55-year-old female who developed acute aortitis of the descending aorta after G-CSF injections for blood stem cells grafting (5). Adiga et al. also reported a 54-year-old male with squamous cell carcinoma of the lung who developed abdominal aortitis following the use of G-CSF (6). Both reports did not describe any symptoms indicating temporal arteries, such as headache in the temples, jaw claudication or visual abnormality.

The influence of G-CSF in patients with autoimmune diseases is controversial; however, some reports have suggested that the use of G-CSF might accelerate the organ damage that occurs in autoimmune diseases. Patients with systemic lupus erythematosus show an exacerbated disease activity after G-CSF treatment (7). In a mouse model, lupus-prone MRL-*lpr/lpr* mice receiving low doses of G-CSF showed an increased glomerular deposition of immunoglobulins and exacerbated lupus disease (8). The implicated Th17 T cells and the increased IL-17 production are together considered to contribute to the pathogenesis of GCA (2). It has been reported that activated neutrophils can also produce IL-17 (9). Accordingly, neutrophils activated by G-CSF may accelerate the onset of GCA via IL-17-mediated inflammation.

The present patient had *HLA-DRB1*04* alleles. The production of *HLA-DRB1*04* alleles is reported to increase in GCA patients (10). When G-CSF treatment is administrated to patients with *HLA-DRB1*04* alleles, we should therefore pay close attention to the potential development of GCA.

Although we could not find any reports in the literature showing cyclic neutropenia patients complicated with GCA, cyclic neutropenia itself might cause the onset of GCA. It has been reported that a patient with cyclic neutropenia de-

veloped cutaneous vasculitis without the use of G-CSF (11). Previous studies also suggest that antigens derived from microbial infection may play some role in the development of GCA (12). In the present case, repeated exposure to such antigens while in the neutropenia state might have served as a trigger for the onset of GCA. It is necessary to accumulate similar cases to improve our understanding of the mechanisms involved in the development of GCA.

The results of cytokine multiplex array are similar to those of previous reports (13, 14). Although Th1 and Th17 cytokines were not significantly elevated in the serum in the present case, we consider that these cytokines might have been activated at inflamed local sites as described in a previous report (15).

In conclusion, we herein reported the first known patient with GCA which developed while using G-CSF as a treatment for cyclic neutropenia. The present case indicates that cyclic neutropenia and the use of G-CSF may affect the development of GCA through an aberrant activation of neutrophils.

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

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