Periaortitis Associated with Anti-neutrophil Cytoplasmic Antibodies Induced by Bevacizumab Combination Therapy

Shuji Murakami, Haruhiro Saito, Miki Ohe, Tetsuro Kondo, Fumihiro Oshita and Kouzo Yamada

Abstract

Drug-induced vessel vasculitis is a rare complication of chemotherapy. In particular, few reports have investigated drug-induced large vessel vasculitis. We herein report the case of a 57-year-old woman with advanced lung adenocarcinoma who developed perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA)-positive periaortitis induced by bevacizumab combination chemotherapy. With the increasing use of combination therapy with bevacizumab, the incidence of vascular complications will potentially increase. A noninfectious fever occurring during chemotherapy might be a sign of vasculitis; therefore, we must ensure that possible periaortitis is not overlooked.

Key words: adenocarcinoma, bevacizumab, p-ANCA, vasculitis


Introduction

Fevers sometimes occur during chemotherapy-induced neutropenia. Under such conditions, an infectious etiology is most likely; however, noninfectious causes of fever should also be considered. Because they exhibit attenuated typical signs and symptoms of inflammation, neutropenic patients with early bacterial infections cannot be reliably distinguished from noninfected patients. Therefore, empirical antibiotic therapy should be administered promptly to all neutropenic patients at the onset of fever. The persistence of a fever despite the administration of initial empiric antibiotic therapy and recovery from neutropenia suggests the presence of a nonbacterial infection such as a drug fever, a tumor-associated fever, collagen disease or allergies.

Case Report

A 57-year-old nonsmoking woman was diagnosed with stage IV lung adenocarcinoma harboring an epidermal growth factor receptor (EGFR) exon 21 gene mutation. She had no history of liver or autoimmune disease and no abnormal findings on computed tomography (CT) scans suggestive of a vascular disorder (Figure A). Gefitinib was administered at a dose of 250 mg/day as first-line chemotherapy.

The gefitinib treatment was discontinued after four months due to substantial increases in the serum transaminase levels (aspartate aminotransferase: 314 U/L; alanine aminotransferase: 583 U/L). Initiation of ursodeoxycholic acid and ammonium glycyrrhizate treatment resulted in gradual decreases in the transaminase levels. In the four weeks after gefitinib withdrawal, the transaminase levels returned to normal; however, the patient’s lung cancer progressed slightly. We initiated second-line treatment using paclitaxel (200 mg/m², day 1)/carboplatin (area under the curve=5, day 1) plus bevacizumab (15 mg/kg, day 1). On the 8th day of chemotherapy, the patient developed a fever of 38.9°C and grade 3 neutropenia; therefore, she was treated with lenograstim (granulocyte colony-stimulating factor (G-CSF)) and antibiotics. On the 9th day, the patient developed thoracic back pain associated with elevation of body temperature. Despite the initial administration of empiric therapy with cefepime along with the addition of levofloxacin, the elevated fever lasted for three weeks.

The results of the patient’s physical examinations were normal, except for some pain in the left side of her neck and upper back that accompanied the fever. Laboratory ex-
aminations showed an elevated lactate dehydrogenase level of 500 IU/L and a C-reactive protein (CRP) level of 20 mg/dL; however, no evidence of any renal disorders such as an elevated serum creatinine level or proteinuria was observed. Immunological tests for anti-nuclear antibodies, anti-double-stranded DNA antibodies, rheumatoid factors and cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) were negative; however, tests for perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) were positive at 32 U/mL (≥10.0 U/mL).

On the 23rd day, a contrast-enhanced CT scan focusing on inflammation revealed soft, thick tissue surrounding the left subclavian artery and thoracic aorta (Figure B) that corresponded to the location of pain. The typical CT images and positive p-ANCA results suggested a diagnosis of peri-aortitis associated with p-ANCA. The patient was treated daily with 30 mg of prednisolone, resulting in complete resolution of the fever and pain over the following day, while the p-ANCA and CRP findings became negative after two weeks. A follow-up CT scan performed at four weeks documented improvement of the thick periaortic tissue (Figure C). The dose of prednisolone was gradually reduced.

Four courses of paclitaxel/carboplatin chemotherapy without bevacizumab were administered at the same dose level as the first course. G-CSF was repeatedly used in the following three courses of chemotherapy. There has been no recurrence of the vasculitis-related symptoms or positive p-ANCA results.

Discussion

There are few reports of drug-induced large vessel vasculitis. Generally, drug-induced vasculitis develops within seven to 21 days after a drug regimen is started (1). Drugs that have been implicated in large vessel vasculitis include penicillin, aminopenicillins, sulfonamide, allopurinol, thiazides, quinolones, hydantoins, propylthiouracil (1) and G-CSF (2). Of the many antineoplastic chemotherapy agents, gemcitabine and platinum-based therapies are most frequently associated with vascular complications. The most common vascular complication is venous thrombosis, while other rare vascular side effects include vasculitis (3).

Antiangiogenic therapies, including bevacizumab, are also associated with vascular complications. Bevacizumab is a recombinant humanized version of the murine anti-human vascular endothelial growth factor (VEGF) monoclonal antibody. The most common vascular side effects of bevacizumab include bleeding, thrombosis and hypertension.

The mechanisms underlying bevacizumab-induced vasculitis are unknown; however, bevacizumab does inhibit VEGF. Tumor neovascularity and chemotherapy-induced apoptosis of endothelial cells seem likely to play a role in the development of vasculitis. Vascular disease occurs as a result of an imbalance between vascular damage and endothelial repair. Endothelial progenitor cells mobilized by angiogenic cytokines, especially VEGF, are essential for endothelial repair. Increased levels of VEGF are correlated with disease activity in ANCA-associated vasculitis. Accordingly, an inability to mobilize endothelial progenitor cells caused by the presence of anti-VEGF receptor antibodies has been postulated to be a risk factor for vascular diseases and seems to aggravate vascular damage induced by chemotherapy. A relationship between chemotherapy with bevacizumab and vasculitis has not been previously demonstrated. However, actual arterial thromboembolic events occur more frequently in patients treated with VEGF receptor-targeting therapies (3.6%) than in control patients (1.7%) (4). Therefore, bevacizumab seems to increase the incidence of vascu-
We diagnosed the current patient with periaortitis based on the presence of increasing neck and back pain with a persistent fever, positive p-ANCA results and diffuse aortic wall thickening on contrast-enhanced CT that was highly suggestive of vasculitis. Only histopathology of the involved site is definitive for the diagnosis of vasculitis. However, if no sites are available for a biopsy, as is the case in patients with large-vessel vasculitis, detecting diffuse vessel wall thickening using ultrasonography, contrast-enhanced CT or magnetic resonance imaging is useful.

Testing for p-ANCA is important when diagnosing drug-induced vasculitis. The specificity of positive p-ANCA tests for the diagnosis of vasculitis is high (up to 99%), whether or not the vasculitis is induced by drugs (5). In patients with drug-induced vasculitis who test positive for ANCA, it is likely that drugs have induced damage in neutrophils (5, 6). However, the exact pathogenic mechanisms involved in drug-induced vasculitis are unknown. ANCA seems to play an important role in the pathogenesis of small vessel vasculitis, and changes involving small vessels have been reported in most of the published cases of p-ANCA-positive vasculitis induced by drugs (5). Therefore, the concurrent occurrence of aortitis and positive p-ANCA seems to be a paradoxical event. However, some reports describe the possibility that p-ANCA induces vasa vasorum vasculitis of large vessels such as the aorta and main branch arteries, which results in the pathological progression of aortitis syndrome (7, 8).

In this case, it is probable that the carboplatin and paclitaxel caused endothelial damage and bevacizumab precipitated the vasculitis. Because no recurrence of chemotherapy-induced vasculitis or re-increases in the p-ANCA level were found during continuous use of carboplatin and paclitaxel, we concluded that the vasculitis in this case was a bevacizumab-related vascular complication. With the increasing use of combination therapy with bevacizumab, the incidence of vascular complications will potentially increase. The occurrence of fever and pain during chemotherapy might be a sign of vasculitis; therefore, physicians must ensure that possible periaortitis is not overlooked.

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

References