Thrombotic Microangiopathy due to Malignant Hypertension Following Corticosteroid Therapy for Microscopic Polyangitis

Katsunobu Yoshioka, Taeka Hattori, Yoshihiro Isaka, Toshimasa Yamaguchi, Keiko Yamagami, Takashi Morikawa, Yoshio Konishi, Toshihiko Sato and Masahito Imanishi

Abstract

A 78-year-old woman was treated with 40 mg of prednisolone for microscopic polyangitis, and favorable effects were observed. However, her blood pressure increased and she developed severe thrombocytopenia. Thrombotic microangiopathy (TMA) due to malignant hypertension was suspected and she was treated with an angiotensin-converting enzyme inhibitor; her platelet count then rose. She showed a close temporal relationship between initiation of corticosteroid therapy and the onset of TMA. Corticosteroid therapy should be used with caution in patients with underlying vascular endothelial damage.

Key words: Thrombotic microangiopathy, Malignant hypertension, Corticosteroid

(Introduction)

Thrombotic microangiopathy (TMA) is a microvascular occlusive syndrome characterized by systemic aggregation of platelets, leading to ischemia in the kidneys and other organs (1). The laboratory characteristics of TMA include thrombocytopenia, microangiopathic hemolytic anemia, and extremely elevated serum levels of lactate dehydrogenase (LDH). Causes of TMA include thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), malignant hypertension, and certain medications. TMA is one of the complications of certain forms of rheumatic disease [eg, systemic lupus erythematosus (2), systemic sclerosis, and overlap syndrome (3)]. However, systemic vasculitis such as polyarteritis nodosa (PAN) (4, 5) or microscopic polyangitis (MPA) are rarely complicated by TMA.

Here, we report a patient who developed TMA due to malignant hypertension following corticosteroid therapy for MPA. Furthermore, the pathogenesis of TMA and the association between corticosteroid therapy and the development of TMA is discussed.

Case Report

A 78-year-old woman visited her family physician complaining of cough, numbness in the lower limbs, congestion of the conjunctiva, jaw claudication and headache. She had been in good health until 1 year previously, when cough and numbness in the lower limbs first appeared. During the following year, congestion of the conjunctiva and headache appeared and numbness in the lower limbs became more severe. Raynaud’s phenomenon was not observed. She thus visited her family physician. She was diagnosed with bronchiectasis and treated with oral antibiotic therapy. No noticeable effects were seen. She was referred and admitted to our hospital in mid-April 2006, for further evaluation and treatment.

At the time of admission, the patient was 147 cm tall and weighed 51 kg. Her blood pressure was 114/70 mmHg and her pulse rate was 60 beats per minute. The bulbar conjunctiva showed intense congestion, and she was diagnosed with scleritis. Inspiratory rales were heard at both lung bases. Sensory examination revealed asymmetrical hypesthesia to pain in the lower limbs. Muscle weakness of lower limbs was noted. Although a nerve conduction study was not per-
formed, these neurological findings were compatible with those of mononeuritis multiplex. Livedo reticularis was observed on the lower limbs. Scleroderma was not observed. The remainder of the physical examination was unremarkable. Laboratory results showed leucocytosis, normochromic normocytic anemia, mild thrombocytopenia, mildly elevated transaminases, and a marked increase in C-reactive protein (CRP) (Table 1). Repeated urinalyses showed (-) to (±) for proteinuria and (-) to (1+) for occult blood. The urinesediment showed 5-9 red blood cells and 10-19 white blood cells per high-power field. A high-titer of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) was detected. Computed tomography of the chest showed old inflammatory changes with no apparent active interstitial pneumonia.

Although histological confirmation was not obtained, a diagnosis of MPA was made on the basis of clinical symptoms such as scleritis, mononeuritis multiplex, and the high-titer of MPO-ANCA. She was treated with 40 mg of prednisolone daily and 50 mg of cyclophosphamide 3 times a week. Her general condition improved after treatment with prednisolone and cyclophosphamide, and CRP levels returned normal on day 10. At that point, her blood pressure began to increase and 4 mg of benidipine therapy was initiated. However, she developed mild thrombocytopenia on day 17 (9.0×10^4/μl). Drug-induced thrombocytopenia was suspected and all medications except for prednisolone and benidipine were discontinued. However, the thrombocytopenia exacerbated and a lower platelet count (3.9×10^4/μl) was seen on day 24. Despite the use of benidipine therapy, her blood pressure increased to more than 200/100 mmHg and serum LDH and total bilirubin levels gradually increased; these symptoms lead us to suspect the likelihood of TMA due to malignant hypertension. Although the results of a urine test were 2+ for proteinuria, there were no clinical symptoms suggesting renal failure or encephalopathy. Although fragmented red blood cells were not detected in peripheral blood, serum haptoglobin was undetectable. Direct and indirect Coombs test results were negative. She was treated with an angiotensin-converting enzyme inhibitor (ACEI), and her platelet count and haptoglobin level gradually increased and serum LDH levels decreased toward normal (Fig. 1). Results of a urine test also became normal. By this time the results of the remaining laboratory tests conducted before induction of ACEI therapy were available and high plasma renin activity (PRA) levels were noted (8.9 ng/ml/h). In addition, PRA level increased to 35.5 ng/ml/h after induction of ACEI therapy. She was discharged on day 63 while receiving 20 mg of prednisolone, and no thrombocytopenia or recurrence of MPA was noted.

### Discussion

The present patient was diagnosed as having MPA based on clinical symptoms such as scleritis, mononeuritis multiplex and a high titer of MPO-ANCA, which is the most useful distinguishing marker between individuals with PAN.
and those with MPA. However, MPO-ANCA does not distinguish MPA from PAN with certainty and without a renal biopsy or angiography, a diagnosis of MPA is not definitive. Thus, the possibility of the diagnosis of PAN in the present case is not completely excluded. However, diagnosis of systemic sclerosis was unlikely because of the lack of symptoms related to systemic sclerosis such as Raynaud’s phenomenon, scleroderma, or negative test for anti-nuclear antibody.

Several medications such as cyclosporine A, tacrolimus, mitomycin, and ticlopidine are known to cause TMA. However, cyclophosphamide and omeprazol have never been reported to cause TMA. Furthermore, despite the discontinuation of these drugs, the thrombocytopenia exacerbated. Thus, drug-induced thrombocytopenia was unlikely in the present case.

The pathogenesis of TMA in systemic vasculitis is unknown but may be related either to TTP, which is characterized by reduced activity of a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13 (ADAMTS 13) caused by either genetic defect (6) or its inhibitor (7), or to other etiologies. The differential diagnosis of etiologies of TMA is difficult because laboratory features of TMA are shared by many diseases. However, prompt and accurate diagnosis of TTP is important because plasmapheresis should be initiated as soon as possible to save lives. Measurement of ADAMTS13 may be useful in differentiating TTP from TMA due to other etiologies (8). However, there is no standardized assay for ADAMTS13 and it is a time-consuming test. The etiology of the present patient was distinguishable from TTP by the moderate thrombocytopenia (8), severe hypertension, and the absence of fever and neurological signs.

Other etiologies of TMA may be related to active vasculitis itself or atherosclerosis-like occlusive vascular injury caused by hypertension or corticosteroid treatment. The present patient showed a close temporal relationship between the initiation of corticosteroid therapy and the onset of TMA. It has been reported that lacunar stroke complicating PAN is caused by thrombosis or fibrosis of the arteries rather than by active vasculitis and that this vascular injury may be aggravated by corticosteroid therapy; this is based on the finding that a close relationship between corticosteroid therapy and the onset of stroke has been seen (9). Furthermore, it has been reported that there is a significant association between antecedent high-dose corticosteroid therapy and the development of sclerodermia renal crisis, one of the causes of TMA (10).

The pathogenesis of sclerodermia renal crisis is not completely understood, but the primary process designates injury to the renal arcuate and interlobular arteries. MPA usually affects arterioles, venules or capillaries. However, it has been reported that medium to small sized vessel (arcuate or interlobular artery) involvement is common in patients with MPA (11). Thus, we speculate that moderate to small arterial endothelial damage in the renal vessels, which results in intimal thickening of the affected vessels, existed in our patient. Platelet counts are usually elevated in inflammatory diseases such as MPA. We speculate that the reason mild thrombocytopenia existed at the time of admission was due to consumption of platelets at the affected vessels. Thus, it is suggested that corticosteroid therapy may trigger the development of microvascular occlusion in patients with un-
derlying moderate to small arterial endothelial damage.

We speculate that narrowed arterial vessels due to vasculitis are the primary cause of decreased cortical blood flow, which was greatly aggravated by the use of corticosteroid therapy. Several mechanisms by which corticosteroid therapy triggered the development of TMA are considered. Corticosteroid therapy has been shown to inhibit prostacyclin (a vasodilator and platelet aggregation inhibitor) production (12) and increase thromboxan A2 (a vasoconstrictor and platelet stimulator of platelet aggregation) production, leading to platelet aggregation and cortical blood flow decrease. The decreased cortical blood flow activates the renin-angiotensin system, which results in endothelial dysfunction and rapid elevation of blood pressure. Furthermore, corticosteroid therapy has been shown to increase angiotensin-converting enzyme activity (13, 14), which additionally activates the renin-angiotensin system. Because the most important factor leading to the development of malignant hypertension is a rapid elevation of blood pressure, we speculate that the use of corticosteroid triggered the onset of malignant hypertension by the mechanisms mentioned above. Typically, malignant hypertension is characterized by severe hypertension and organ damage including progressive heart failure, renal failure and encephalopathy. We believe we were able to treat our patient before she developed the typical symptoms of malignant hypertension.

Therapeutic strategies for TMA due to malignant hypertension consist of rapid control of blood pressure using renin-angiotensin system antagonists such as ACEI or angiotensin II antagonists. From the preventive point of view, antiplatelet drug administration at the same time as corticosteroid therapy may reduce the risk of development of corticosteroid-induced renal artery occlusion in patients with underlying vascular endothelial damage.

In summary, we encountered a patient who developed TMA due to malignant hypertension following corticosteroid therapy for MPA. Corticosteroid therapy should be used in caution in patients with underlying vascular endothelial damage.

References


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