Two Cases of Acute Ischemic Stroke Associated with Iron Deficiency Anemia due to Bleeding from Uterine Fibroids in Middle-aged Women

Hiroyuki Naito, Hiromitsu Naka, Yuhei Kanaya, Yu Yamazaki and Hiroshi Tokinobu

Abstract

We herein report two cases of acute ischemic stroke associated with iron deficiency anemia (IDA) due to bleeding from uterine fibroids. Anemia is not generally recognized as a risk factor for stroke. The physiological mechanisms that may factor in the development of ischemic stroke in patients with IDA include thrombocytosis, hypercoagulable state, and anemic hypoxia. In our two cases, IDA was considered to be the cause of ischemic stroke because all other known causes of stroke were ruled out. In patients with ischemic stroke due to anemia, early treatment of the anemia is important to prevent stroke recurrence.

Key words: ischemic stroke, anemia, iron deficiency anemia

(Intern Med 53: 2533-2537, 2014)
(DOI: 10.2169/internalmedicine.53.2620)

Introduction

Ischemic stroke may be caused by thrombotic, embolic, or hemodynamic events and may be classified as a lacunar infarction, atherothrombotic infarction, cardiogenic embolism, or stroke with other determined or undetermined etiology (1). In young adults, ischemic stroke is most commonly classified as “stroke with other determined etiology” (including arterial dissection, antiphospholipid antibody syndrome, moyamoya disease, and vasculitis syndrome) or “stroke with undetermined etiology.” To prevent recurrence of ischemic stroke, it is important to identify the cause and the type of stroke, manage the associated risk factors, and administer antithrombotic therapy. Numerous studies have reported the most common risk factors for ischemic stroke (2, 3). Although an association between anemia and acute ischemic stroke has been reported, anemia is not well recognized as a potential cause of stroke. We herein report two cases of ischemic stroke in middle-aged women that were considered to be caused by iron deficiency anemia (IDA) due to bleeding from uterine fibroids. IDA is relatively common in young adults and therefore should be considered as a potential cause of ischemic stroke in the population.

Case Reports

Case 1

A 42-year-old woman presented to another hospital with left facial and left upper extremity weakness. She was diagnosed with acute ischemic stroke based on brain magnetic resonance imaging (MRI) findings and was referred to our hospital. She had a three-year history of menorrhagia and a one-year history of IDA, and complained of a recent increase in fatigue. Her recent menstrual cycles were shortened to two weeks with increased amounts of bleeding. She had no other medical history and was not taking any medications. She did not have hypertension, dyslipidemia, or diabetes mellitus. There was no family history of neurological or hematological conditions. Her neurological examination revealed mild dysarthria and left central facial weakness. Laboratory testing showed a low hemoglobin concentration (5.3 g/dL), low hematocrit (20.4%), low mean corpuscular volume (59.5 fL), low mean corpuscular hemoglobin (15.5 pg/cell), normal platelet count (26.0×10⁴/μL), high D-dimer level (2.0 μg/mL), low serum iron concentration (11 μg/dL), high unsaturated iron-binding capacity (359 μg/dL), and low
Figure 1. Case 1. (A) Brain MRI. Diffusion-weighted (DWI) and fluid-attenuated inversion recovery (FLAIR) images showed hyperintense lesions while the apparent diffusion coefficient (ADC) maps showed hypointense lesions in the same areas, indicating an acute infarction in the right cerebellar hemisphere, right frontal lobe, and left frontal lobe. (B) Contrast-enhanced pelvic CT (sagittal view) depicted a submucosal uterine fibroid. MRI without contrast of the pelvis. The T1WI image (upper side) showed a hypointense lesion and the T2WI image (bottom side) showed a mainly hypointense lesion, indicating a uterine fibroid without necrosis, hematoma, or invasion.

serum ferritin level (4.0 ng/mL). Based on these findings, she was diagnosed with IDA. The patient’s blood cell count, general chemistry panel, and blood coagulation results were within normal limits. She had a high CA-125 level (185 U/mL), but the other tumor marker levels were normal. Her erythrocyte sedimentation rate was normal, and tests for protein S, protein C, anti-nuclear and anti-cardiolipin antibodies were all negative. Brain MRI showed an acute infarction in the right cerebellar hemisphere, right frontal lobe, and left frontal lobe (Fig. 1A). Magnetic resonance angiography (MRA) showed no evidence of stenosis or occlusion of the carotid or intracranial arteries. All other known causes of stroke were ruled out by additional investigations, including carotid artery Doppler ultrasonography, transthoracic echocardiography, lower limb ultrasonography, Holter electrocardiography (ECG), and computed tomography (CT) angiography (CTA). Abdominal ultrasonography, contrast-enhanced CT (Fig. 1B) and contrast-enhanced MRI showed a uterine fibroid. The endometrial and vaginal cytology and endometrial histology were negative for malignancy. Based on these results, she was diagnosed with IDA due to bleeding from a uterine fibroid. We initially considered a diagnosis of
Case 2

A 42-year-old woman presented to our hospital after diagnosis of a subacute cerebral infarction based on brain MRI findings. Eleven days previously, she had experienced a half-hour episode of right upper and lower extremity weakness, numbness, and aphasia which had occurred soon after the end of her menstrual period. She had no remarkable past medical history except for a two-year history of menorrhagia. She was not taking any medications, including iron replacement therapy or oral contraceptives. Her mother had

Trousseau’s syndrome (due to the high D-dimer and CA-125 levels, uterine mass, and bilateral multiple cerebral infarctions) and started anticoagulation therapy with heparin. She refused a blood transfusion for her anemia and received intravenous iron therapy. Her anemia and neurological dysfunction gradually improved, and there was no recurrence of stroke. After the uterine fibroid was diagnosed and all other known causes of stroke were ruled out, anticoagulation therapy was discontinued. Her D-dimer level returned to normal within one week following the end of anticoagulation therapy and remained normal on subsequent testing. The uterine fibroid was surgically removed, and the diagnosis was confirmed by a postoperative histopathological examination. Eight months after surgery, the patient’s anemia had completely resolved (hemoglobin concentration: 14.4 g/dL). There was no evidence of recurrence of ischemic stroke at her 15-month follow-up.

Case 2

A 42-year-old woman presented to our hospital after diagnosis of a subacute cerebral infarction based on brain MRI findings. Eleven days previously, she had experienced a half-hour episode of right upper and lower extremity weakness, numbness, and aphasia which had occurred soon after the end of her menstrual period. She had no remarkable past medical history except for a two-year history of menorrhagia. She was not taking any medications, including iron replacement therapy or oral contraceptives. Her mother had

Figure 2. Case 2. (A) Brain MRI 11 days after the neurological symptoms. DWI and FLAIR images, showing hyperintense lesions, indicated a subacute infarction in the left basal ganglia and left frontal lobe. (B) Contrast-enhanced pelvic CT (coronal and sagittal view) depicted a submucosal uterine fibroid without hematoma.
a history of uterine fibroids. The patient’s neurological examination was normal. She had untreated risk factors for vascular disease including hypertension, dyslipidemia (high low-density lipoprotein concentration: 185 mg/dL) and diabetes mellitus (high hemoglobin A1c concentration: 7.0%). Laboratory testing indicated a hemoglobin concentration at the lower end of the normal range (11.6 g/dL), low hematocrit (37.5%), low mean corpuscular volume (69.1 fl), low mean corpuscular hemoglobin (21.4 pg/cell), high platelet count (429x10^4/μL), and normal D-dimer level (0.4 μg/mL) indicating microcytic hypochromic anemia and thrombocytosis.

The patient’s blood cell count, general chemistry panel, and blood coagulation test results were within the normal limits. Brain MRI showed a subacute infarction in the left basal ganglia and left frontal lobe (Fig. 2A). MRA and carotid artery Doppler ultrasonography showed no evidence of stenosis or occlusion of the carotid or intracranial arteries. ECG showed no arrhythmia. We prescribed clopidogrel (75 mg daily) and controlled her vascular risk factors on an outpatient basis. After four months, her anemia had worsened (hemoglobin concentration: 9.2 g/dL), and clopidogrel was stopped. She refused oral iron therapy due to severe gastrointestinal symptoms. Her anemia continued to worsen but there was no further evidence of neurological dysfunction.

After nine months, the patient was hospitalized to investigate her anemia and determine the cause of her ischemic stroke. Repeat brain MRI showed old infarctions in the left basal ganglia and the left frontal lobe, but no new infarctions. MRA showed no abnormalities of the carotid or intracranial arteries. T2*-weighted and gradient-recalled echo susceptibility-weighted brain MRI and magnetic resonance venography (MRV) showed no abnormalities of the cerebral venous system. Laboratory testing showed a remarkable decrease in hemoglobin concentration (9.1 mg/dL), high platelet count (48.0x10^4/μL), low serum iron concentration (14 μg/dL), high unsaturated iron-binding capacity (400 μg/dL), low serum ferritin level (3.6 ng/mL), and a high transferrin saturation (329.0 mg/dL). Based on these findings, she was diagnosed with IDA. The patient’s hemoglobin electrophoresis, tumor marker levels, erythrocyte sedimentation rate, and blood coagulation test results were within the normal limits. Brain MRI showed a subacute infarction in the left basal ganglia and left frontal lobe (Fig. 2A). MRA and carotid artery Doppler ultrasonography showed no evidence of stenosis or occlusion of the carotid or intracranial arteries. ECG showed no arrhythmia. We prescribed clopidogrel (75 mg daily) and controlled her vascular risk factors on an outpatient basis. After four months, her anemia had worsened (hemoglobin concentration: 9.2 g/dL), and clopidogrel was stopped. She refused oral iron therapy due to severe gastrointestinal symptoms. Her anemia continued to worsen but there was no further evidence of neurological dysfunction.

After nine months, the patient was hospitalized to investigate her anemia and determine the cause of her ischemic stroke. Repeat brain MRI showed old infarctions in the left basal ganglia and the left frontal lobe, but no new infarctions. MRA showed no abnormalities of the carotid or intracranial arteries. T2*-weighted and gradient-recalled echo susceptibility-weighted brain MRI and magnetic resonance venography (MRV) showed no abnormalities of the cerebral venous system. Laboratory testing showed a remarkable decrease in hemoglobin concentration (9.1 mg/dL), high platelet count (48.0x10^4/μL), low serum iron concentration (14 μg/dL), high unsaturated iron-binding capacity (400 μg/dL), low serum ferritin level (3.6 ng/mL), and a high transferrin saturation (329.0 mg/dL). Based on these findings, she was diagnosed with IDA. The patient’s hemoglobin electrophoresis, tumor marker levels, erythrocyte sedimentation rate, and blood coagulation test results were within the normal limits. Brain MRI showed a subacute infarction in the left basal ganglia and left frontal lobe (Fig. 2A). MRA and carotid artery Doppler ultrasonography showed no evidence of stenosis or occlusion of the carotid or intracranial arteries. ECG showed no arrhythmia. We prescribed clopidogrel (75 mg daily) and controlled her vascular risk factors on an outpatient basis. After four months, her anemia had worsened (hemoglobin concentration: 9.2 g/dL), and clopidogrel was stopped. She refused oral iron therapy due to severe gastrointestinal symptoms. Her anemia continued to worsen but there was no further evidence of neurological dysfunction.

After nine months, the patient was hospitalized to investigate her anemia and determine the cause of her ischemic stroke. Repeat brain MRI showed old infarctions in the left basal ganglia and the left frontal lobe, but no new infarctions. MRA showed no abnormalities of the carotid or intracranial arteries. T2*-weighted and gradient-recalled echo susceptibility-weighted brain MRI and magnetic resonance venography (MRV) showed no abnormalities of the cerebral venous system. Laboratory testing showed a remarkable decrease in hemoglobin concentration (9.1 mg/dL), high platelet count (48.0x10^4/μL), low serum iron concentration (14 μg/dL), high unsaturated iron-binding capacity (400 μg/dL), low serum ferritin level (3.6 ng/mL), and a high transferrin saturation (329.0 mg/dL). Based on these findings, she was diagnosed with IDA. The patient’s hemoglobin electrophoresis, tumor marker levels, erythrocyte sedimentation rate, and blood coagulation test results were within the normal limits. Brain MRI showed a subacute infarction in the left basal ganglia and left frontal lobe (Fig. 2A). MRA and carotid artery Doppler ultrasonography showed no evidence of stenosis or occlusion of the carotid or intracranial arteries. ECG showed no arrhythmia. We prescribed clopidogrel (75 mg daily) and controlled her vascular risk factors on an outpatient basis. After four months, her anemia had worsened (hemoglobin concentration: 9.2 g/dL), and clopidogrel was stopped. She refused oral iron therapy due to severe gastrointestinal symptoms. Her anemia continued to worsen but there was no further evidence of neurological dysfunction.

After nine months, the patient was hospitalized to investigate her anemia and determine the cause of her ischemic stroke. Repeat brain MRI showed old infarctions in the left basal ganglia and the left frontal lobe, but no new infarctions. MRA showed no abnormalities of the carotid or intracranial arteries. T2*-weighted and gradient-recalled echo susceptibility-weighted brain MRI and magnetic resonance venography (MRV) showed no abnormalities of the cerebral venous system. Laboratory testing showed a remarkable decrease in hemoglobin concentration (9.1 mg/dL), high platelet count (48.0x10^4/μL), low serum iron concentration (14 μg/dL), high unsaturated iron-binding capacity (400 μg/dL), low serum ferritin level (3.6 ng/mL), and a high transferrin saturation (329.0 mg/dL). Based on these findings, she was diagnosed with IDA. The patient’s hemoglobin electrophoresis, tumor marker levels, erythrocyte sedimentation rate, and total homocysteine level were normal, and testing for protein S, protein C, anti-nuclear, and anti-cardiolipin antibodies was negative. All other known causes of stroke were ruled out by additional investigations, including carotid artery Doppler ultrasonography, transthoracic echocardiography, transesophageal echocardiography, Holter ECG, coronary CT, CTA, and upper and lower gastrointestinal endoscopy. She was diagnosed with IDA due to bleeding from a uterine fibroid based on abdominal ultrasonography and contrast-enhanced CT findings (Fig. 2B). The uterine fibroid was surgically removed, and the diagnosis was confirmed by a postoperative histopathological examination. As soon as her anemia improved after surgery, her thrombocytosis improved (platelet count, 27.2x10^4/μL) and there was no recurrence of ischemic stroke.

Discussion

As the management of stroke and the risk factors for stroke recurrence vary according to the type of stroke, it is important to determine the cause of ischemic stroke. Anemia is recognized as a risk factor for ischemic stroke in children (4, 5), and ischemic stroke has been reported in adults with sickle-cell anemia (6). Recent studies reported significant associations between anemia and larger infract territory, higher one-year mortality, and worse long-term outcome in patients with ischemic stroke (7-9). However, anemia is not well recognized as a risk factor for ischemic stroke because only a few individual cases and small-scale studies have been reported. In Japan, 8.9% of all strokes occur in adults aged less than 50 years. In these patients, the most frequent type of stroke is “stroke with other determined etiology,” accounting for 36% of all cases (10). Awareness of the association between IDA and ischemic stroke is important for the treatment of ischemic stroke in young adults and for the prevention of stroke recurrence. In our two cases, no new neurological deficits occurred before the development of IDA or after the resolution of IDA, thus suggesting that the stroke resulted from IDA. These cases show that IDA due to bleeding from uterine fibroids should be considered as a potential cause of ischemic stroke with no other known cause.

The association between IDA and ischemic stroke has been studied more frequently in children than in young adults. Physiological mechanisms that may play a role in the development of ischemic stroke in patients with IDA include thrombocytosis, hypercoagulable state, and anemic hypoxia. Low iron levels cause disinhibition of megakaryocyte activity (11), thus resulting in secondary thrombocytosis and a hypercoagulable state (12). Microcytic red blood cells have altered deformability, which increases the blood viscosity and may increase the risk of venous thrombosis (13). The decreased oxygen-carrying capacity of the erythrocytes results in anemic hypoxia, and anemic patients need increased blood flow to the brain to compensate for the lack of oxygen in the blood. This increased blood flow can cause vascular endothelial damage, resulting in thrombus formation. The authors of a previous report of three cases of ischemic stroke in patients with IDA considered that the thrombocytosis could have acted synergistically with the anemia to promote thrombogenesis in the carotid artery, especially with underlying atherosclerotic disease (14). The subcortical border-zone areas are particularly susceptible to ischemia when there is reduced cerebral blood flow and oxygen supply. In previously reported patients with cerebral infarction associated with anemia due to acute bleeding (15, 16), infarction was frequent in watershed areas and was most commonly caused by atherothrombosis. In case 2, IDA was not present (hemoglobin concentration, 11.6 g/dL) at the time of her neurological symptoms. There is currently insufficient evidence and insufficient understanding of the underlying mechanisms to determine the relationship between sub-
clinical iron deficiency and cerebral infarction. However, it is known that thrombocytosis is frequent in patients with mild IDA (17), and such thrombocytosis may play a role in intravascular thrombogenesis. Additionally, the risk factor of paradoxical embolic stroke with pulmonary arteriovenous malformation (AVM) has been previously reported to be associated with low serum iron concentration (18). This report indicates that iron deficiency is associated with exuberant platelet aggregation to serotonin (5HT). In case 2, the patient had a consistently high platelet count (42.9×10^9/μL) from her initial visit to our hospital. As soon as her IDA improved after surgery, the reactive thrombocytosis improved (platelet count: 27.2×10^9/μL). We believe that this result is compatible with the platelet aggregation secondary to iron deficiency.

Cerebral infarction in patients with uterine fibroids has previously been reported to be associated with paradoxical cerebral embolism, pulmonary AVM, and cerebral venous thrombosis (CVT) (18-20). In both our cases, no pulmonary AVM was detected on chest CT angiography. We did not check for a patent foramen ovale (PFO) on transesophageal echocardiography in case 1, but lower limb ultrasonography showed no evidence of deep venous thrombosis. T2-weighted images have been reported to be useful for the detection of acute CVT, with an occluded venous sinus showing as a hypointense area (90% sensitivity) (21). In case 2, the patient had a consistently high platelet count (42.9×10^9/μL) from her initial visit to our hospital. As soon as her IDA improved after surgery, the reactive thrombocytosis improved (platelet count: 27.2×10^9/μL). We believe that this result is compatible with the platelet aggregation secondary to iron deficiency.

In conclusion, in patients with acute ischemic stroke and anemia, it is important to consider anemia as the cause of stroke to prevent stroke recurrence. Despite our report of two cases, the reason why few patients result in ischemic stroke is not clear, although many patients present with clinical/subclinical iron deficiency anemia. Therefore, further studies of similar cases are necessary to understand the underlying etiology.

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

References