

[CASE REPORT]

Embolic Stroke Due to a Mural Thrombus in the Ascending Aorta Following Cisplatin-based Chemotherapy

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Abstract:

A 59-year-old woman with small-cell lung carcinoma achieved tumor disappearance after cisplatin-based chemotherapy (CBC) and radiation treatment but subsequently experienced right hemiparesis and aphasia. Brain magnetic resonance imaging revealed a left middle cerebral artery territory acute infarction and left internal carotid artery occlusion. Ultrasonography revealed a mobile thrombus in the left common and internal carotid arteries, and contrast computed tomography revealed a mural thrombus in the ascending aorta. Based on these findings, embolic stroke due to aortic mural thrombus following CBC was diagnosed. Aortic mural thrombus is a rare complication of CBC but carries a risk of embolic stroke.

Key words: cisplatin, aortic mural thrombus, embolic stroke, small-cell lung carcinoma

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Introduction

Small-cell lung carcinoma (SCLC) is generally thought to be the most malignant subtype of lung cancer. The standard treatment is cisplatin-based chemotherapy (CBC) combined with radiation therapy for the limited stage and CBC alone for the extensive stage (1). However, cisplatin use carries a potential risk of thromboembolism (2, 3).

We herein report a patient with SCLC who was successfully treated with CBC and radiation but subsequently experienced an ischemic stroke due to a mural thrombus in the ascending aorta. Aortic mural thrombus, especially in the ascending aorta, is a rare complication of CBC but poses a risk of serious embolic stroke.

Case Report

A 59-year-old right-handed woman with stage IIIB (T3N2 M0) SCLC in the right middle lobe (Fig. 1A) was successfully treated with 4 standard courses of cisplatin-etoposide therapy (cisplatin 80 mg/m²/day on day 1 and etoposide 100 mg/m²/day on days 1-3 every 3 weeks for 4 cycles) combined with a total of 60 Gy of radiation, which achieved complete disappearance of the tumor (Fig. 1B). However,

right hemiparesis and aphasia developed two days after the final chemotherapy course. She was admitted to a local hospital but was transferred the next day to our hospital, where she had received her chemotherapy.

A neurological examination revealed left conjugate deviation, right complete hemiparesis, including the face, and motor-dominant aphasia; her National Institute of Health stroke scale (NIHSS) score was 20. Tendon reflexes in the right upper and lower extremities were slightly increased, and Babinski reflex was positive on the right side. Vital signs were normal; blood pressure was 136/42 mmHg, heart rate was regular and 72/min, respiratory rate was 14/min, and body temperature was 37.1°C. Brain magnetic resonance imaging (MRI) performed in the local hospital (day 1) showed an acute infarction in the left middle cerebral artery (MCA) territory (Fig. 2A-F), non-terminal occlusion of the left internal carotid artery (ICA) and probable main trunk occlusion of the left MCA (Fig. 2G, H). An imaging mismatch between diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) was evident at the time. Previous contrast-enhanced brain MRI examined before the CBC revealed that the left ICA and left MCA appeared to be normal (Fig. 3). This suggested that the tandem ICA-MCA occlusions might be embolic.

Brain MRI on admission (day 2) showed an acute infar-

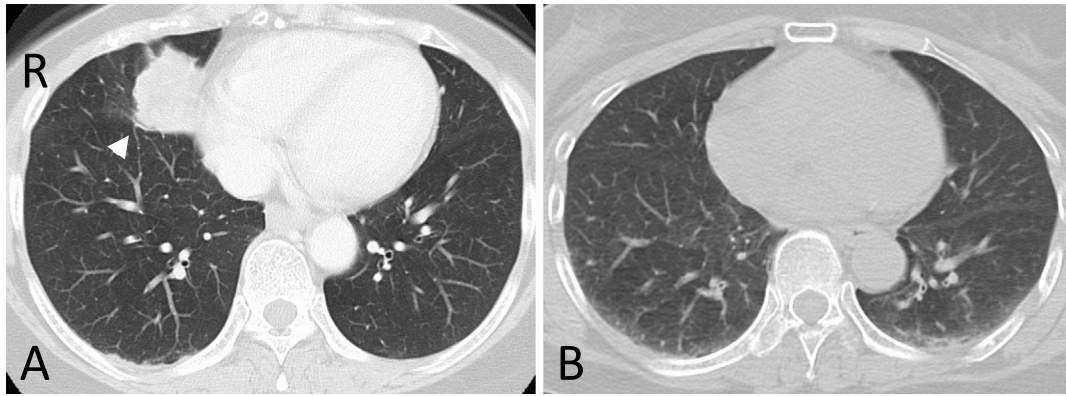


Figure 1. Computed tomography (CT) of the chest before and after cisplatin-based chemotherapy. Contrast chest CT prior to chemotherapy (A) shows the lung cancer in the right middle lobe (white arrowhead). Non-contrast chest CT immediately after the final chemoradiotherapy course (B) shows that the tumor in the right middle lobe has completely vanished. R indicates right side A through B.

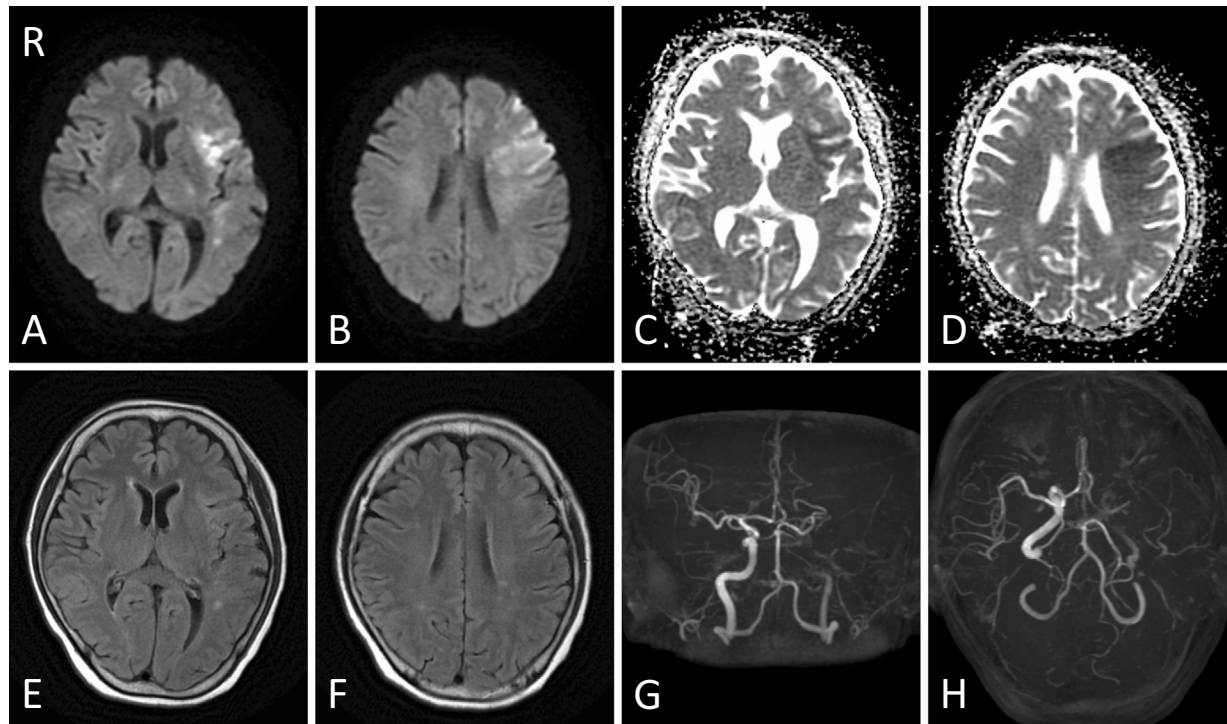


Figure 2. Magnetic resonance imaging of the brain on day 1. Note the acute brain infarction in the left middle cerebral artery (MCA) territory, showing a high signal intensity on diffusion-weighted imaging (A, B) and low signal intensity on apparent diffusion coefficient maps (C, D). The ischemic area does not show obvious signal changes on fluid-attenuated inversion recovery, except for the left insula cortex (E, F). Magnetic resonance angiography indicates non-terminal occlusion of the left internal carotid artery and probable main trunk occlusion of the left MCA (G, H). R indicates right side A through H.

tion in the anterior territory of the left MCA (Fig. 4A-F) and complete occlusion of the left ICA-MCA (Fig. 4G, H). The DWI-FLAIR mismatch was not observed anymore. A blood cell count on admission showed moderate anemia and the following findings: white blood cells (WBCs) 3,900/ μ L, red blood cells (RBCs) 282×10^4 / μ L, hemoglobin 8.6 g/dL and platelets 15.8×10^4 / μ L. Blood biochemistry revealed slightly elevated levels of glucose (141 mg/dL), HbA1c

(7.6%) and triglyceride (206 mg/dL), low levels of high-density lipoprotein cholesterol (30 mg/dL), almost normal levels of low-density lipoprotein cholesterol (122 mg/dL) and normal levels of N-terminal pro-brain natriuretic peptide (72 pg/mL). D-dimer levels were slightly increased (2.4 μ g/mL), but protein C levels were normal: protein C antigen 100% (normal range: 70-150%) and protein C activity 114% (normal range: 64-146%). Protein S levels were also normal:

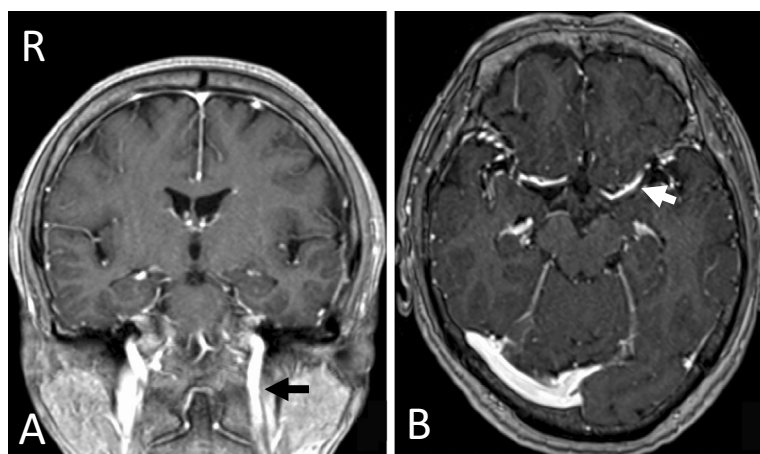


Figure 3. Contrast-enhanced magnetic resonance imaging of the brain before chemotherapy. Contrast-enhanced T1-weighted coronal (A) and axial (B) images show that the left internal carotid (black arrow) and middle cerebral (white arrow) arteries appear to be normal. R indicates right side A through B.

protein S antigen 98% (normal range: 65-135%), protein S free antigen 104% (normal range: 60-104%) and protein S activity 99% (normal range: 56-126%). Antithrombin-III levels were unremarkable: 93.5% (normal range: 70-130%). Antiphospholipid antibodies were negative.

Physiological function tests were performed on days 3-4. A Holter electrocardiogram showed no atrial fibrillation. Transthoracic echocardiography indicated neither valvular abnormalities nor left atrial enlargement (left atrial diameter: 24 mm), and an additional microbubble test with abdominal compression in substitution for the Valsalva maneuver revealed no right-left shunt. Transesophageal echocardiography was not performed in order to avoid any risk of aspiration pneumonia because of her post-chemotherapy condition. Venous ultrasonography revealed asymptomatic distal deep vein thrombosis in the right fibular vein. Carotid ultrasonography showed a mobile thrombus extending from the left common carotid artery to the ICA. Contrast computed tomography (CT) on day 4 revealed a massive thrombus within the left common carotid and internal carotid arteries (Fig. 5A) and a mural thrombus attached to the calcified lesion of the ascending aorta (Fig. 5B, C), which had not been observed before chemotherapy (Fig. 5D). Brain CT on day 8 demonstrated hemorrhagic infarction in the left MCA territory (Fig. 5E). Based on these findings, cardiogenic embolism, including paradoxical embolism, was unlikely, and aortic mural thrombus was considered a potential embolic source in the patient. Embolic stroke due to an aortic mural thrombus following CBC was therefore diagnosed.

After admission she received 60 mg/day of intravenous edaravone, a free radical scavenger, and intravenous heparin was begun in order to achieve 1.5-fold prolongation of the activated partial thromboplastin time over the baseline for the aortic mural thrombus. Due to progressive pancytopenia on day 4 (WBCs $1,600/\mu\text{L}$, RBCs $253 \times 10^4/\mu\text{L}$, hemoglobin 7.6 g/dL, platelets $7.9 \times 10^4/\mu\text{L}$) resulting from the final

course of chemotherapy, surgical thrombectomy was not performed. Contrast CT on day 17 revealed complete disappearance of the aortic mural thrombus (Fig. 5F) with no additional whole-body embolisms observed, and the antithrombotic therapy was changed to aspirin 81 mg/day.

She was transferred to a rehabilitation facility on day 42. After six months of rehabilitation, she still exhibited right hemiparesis and motor-dominant aphasia (NIHSS score 13 and modified Rankin scale 4). Brain MRI at 12 months after the stroke onset showed an old infarction in the left MCA territory (Fig. 6A, B), which was basically similar to the previously observed lesion, and occlusion of the left ICA-MCA (Fig. 6C, D). She showed no cancer recurrence or further thromboembolic events for at least 18 months and had a normal D-dimer level despite no anticoagulant use.

Discussion

Machleder et al. reviewed 10,671 consecutive autopsies and identified 48 cases of nonaneurysmal aortic mural thrombus, of which 38 were in the abdominal aorta, 1 was in the thoracic aorta, and 9 were in both (4). Pagni et al. analyzed 14 patients with symptomatic thoracic aortic mural thrombus and found that only 1 patient had a mural thrombus in the ascending aorta (5). These findings point to the rarity of a nonaneurysmal mural thrombus in the ascending aorta.

An ischemic stroke, particularly an embolic stroke, in patients with active cancer may be a sign of Trousseau syndrome, which is thought to arise from the hypercoagulability associated with cancer (6). This disorder generally has a poor prognosis, as seen in the median survival time of 4.5 months (7). Although the present patient suffered from cancer and eventually experienced an ischemic stroke, Trousseau syndrome was unlikely to be the cause of the stroke for the following reasons: first, chemoradiotherapy had achieved

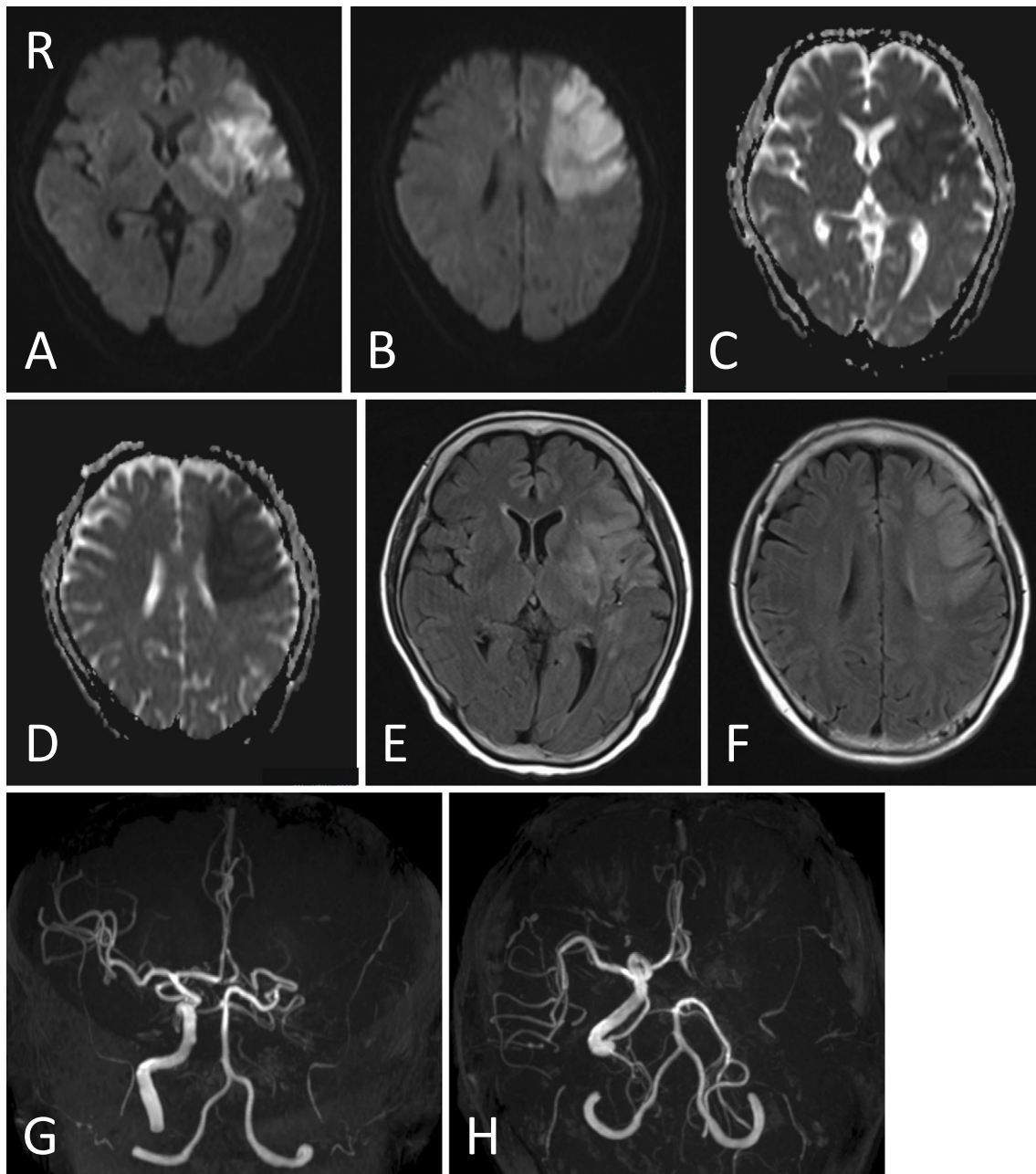


Figure 4. Magnetic resonance imaging of the brain on day 2. Note the acute brain infarction in the anterior territory of the left middle cerebral artery (MCA), showing a high signal intensity on diffusion-weighted imaging (A, B) and low signal intensity on apparent diffusion coefficient maps (C, D). The ischemic lesion also exhibits a high signal intensity on fluid-attenuated inversion recovery (E, F). Magnetic resonance angiography indicates complete occlusion of the left internal carotid artery and the left MCA, but cross flow through anterior communicating artery supplies the left anterior cerebral artery (G, H). R indicates right side A through H.

complete resolution of the lung tumor prior to the stroke onset; second, no thromboembolic events had occurred for more than 18 months during aspirin therapy following the disappearance of the aortic mural thrombus although the initial treatment began with heparin; finally, the D-dimer level had remained normal despite the discontinuation of anticoagulants.

Standard chemotherapy for SCLC consists of a cisplatin-based regimen (1), but cisplatin is known to be a risk factor of thromboembolism. Lee et al. analyzed 277 patients with

SCLC who received chemotherapy, of whom 218 received cisplatin, and found that CBC was an independent risk factor of thromboembolism, as indicated by a hazard ratio of 4.36 (2). Moore et al. also analyzed 932 cancer patients treated with CBC and discovered an extremely high incidence of 18.1% for thromboembolisms, most of which were deep vein thromboses and pulmonary embolisms; arterial embolisms were rare (3). Although the pathogenesis of cisplatin-related arterial embolisms remains uncertain, endothelial cell damage, as indicated by von Willebrand factor

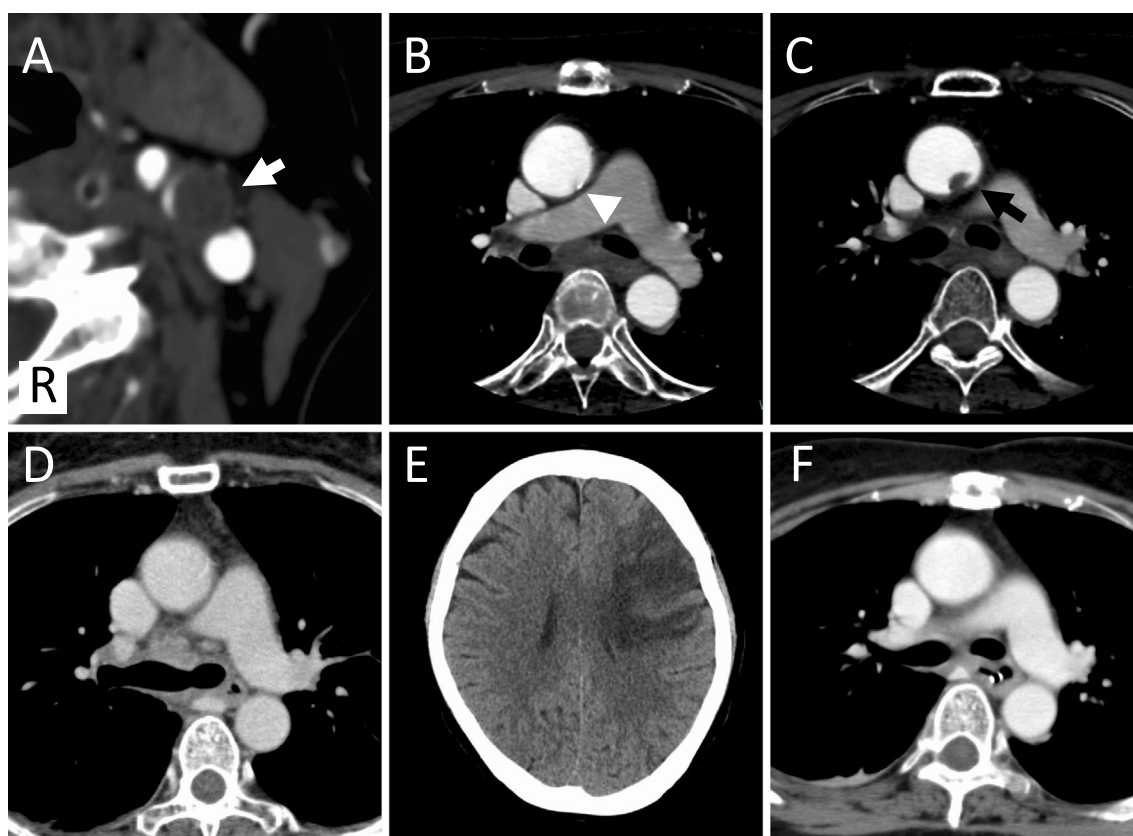


Figure 5. Computed tomography (CT) of the brain, neck and chest. Contrast neck CT on day 4 (A) shows the massive thrombus in the left internal carotid artery (white arrow). Contrast chest CT on day 4 (B, C) demonstrates the aortic mural thrombus (black arrow) attached to the calcified lesion of the ascending aorta (white arrowhead). There is no mural thrombus in the ascending aorta on contrast chest CT examined before chemotherapy (D). Brain CT on day 8 (E) displays hemorrhagic infarction in the left middle cerebral artery territory. Contrast chest CT on day 17 (F) shows the disappearance of the aortic mural thrombus. R indicates right side A through F.

release, may be a contributing factor (8). Endothelial damage was not confirmed in the present patient, because the von Willebrand factor level was not examined. However, the aortic calcified lesion might suggest atherosclerotic endothelial impairment, and CBC together with atherosclerosis might have generated mural thrombus in the present patient.

Thus far, only two cases of aortic mural thrombus associated with CBC in the ascending aorta have been reported (9, 10), and the characteristics of the patients are summarized in Table. A patient reported by Moorjani et al. was undergoing CBC for bladder carcinoma and was incidentally found to have an asymptomatic aortic mural thrombus on three-dimensional CT of the chest (9). Surgical thrombectomy disclosed mobile thrombus adherent to the ascending aorta along with a separate aortic ulcer (9). Similar to our patient, the atherosclerotic endothelial impairment together with cisplatin-induced endothelial damage may have caused the aortic mural thrombus in that patient. Another patient reported by Yagyu et al. also had an asymptomatic aortic mural thrombus after pre-operative CBC for gastric cancer, which was incidentally found on enhanced CT for an evaluation of the response to chemotherapy. That patient also had protein C deficiency, a risk factor of hyper-

coagulability (10). Both patients were asymptomatic, and neither had an ischemic stroke. Atherosclerosis risk factors were not mentioned in either case. The present patient did not have any coagulation disorders as far as we found but was suggested to have potential atherosclerotic endothelial damage of the ascending aorta. Although arterial thrombosis is a rare complication after CBC, cisplatin-induced endothelial damage in combination with additional factors, such as coagulation disorder and atherosclerosis, may cause aortic mural thrombus.

The present report is the first to describe an embolic stroke due to a mural thrombus attached to the ascending aorta following CBC. Physicians should be aware of aortic mural thrombus as a rare cause of ischemic stroke in patients treated with CBC, given the wide use of cisplatin against various cancers aside from SCLC.

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

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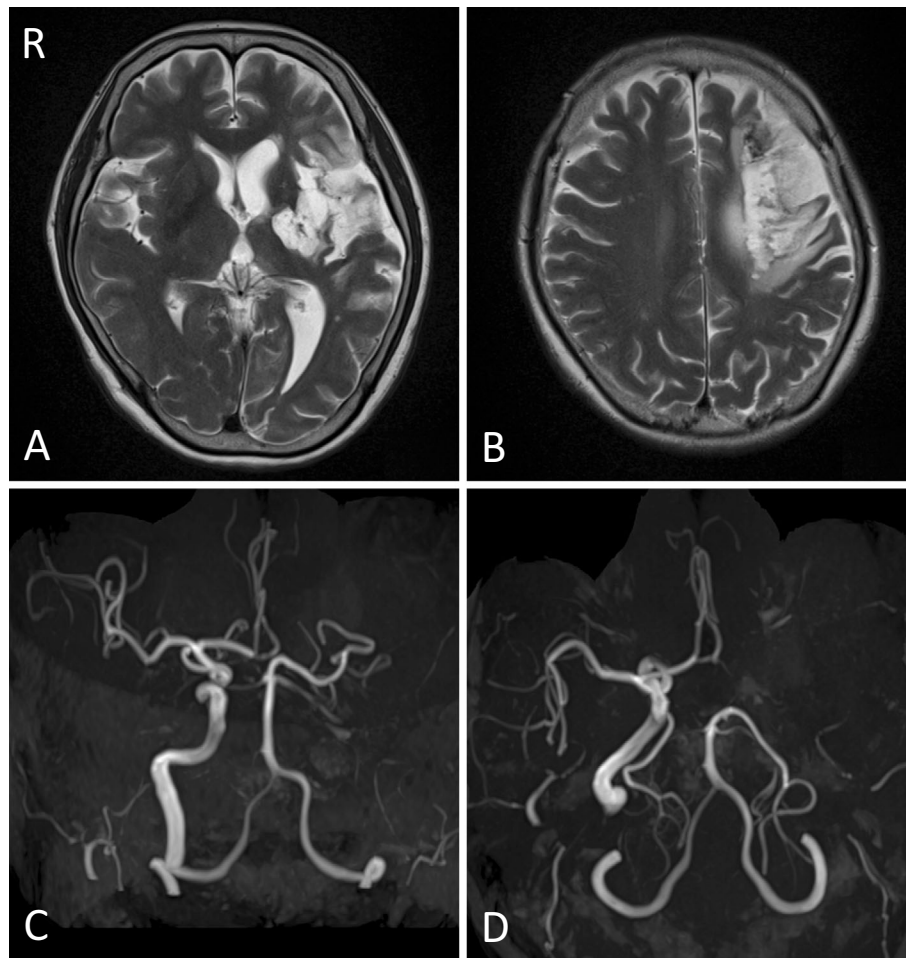


Figure 6. Magnetic resonance imaging at 12 months after stroke. T2-weighted images (A, B) show old infarction in the left middle cerebral artery (MCA) territory. Magnetic resonance angiography shows occlusions of the left internal carotid artery and the left MCA (C, D). R indicates right side A through D.

Table. Clinical Characteristics of Patients with Mural Thrombus in the Ascending Aorta Following Cisplatin-based Chemotherapy.

	Age	Sex	Cancer	Symptoms	Coagulation disorder	Atherosclerosis	Initial treatment	Long-term treatment
Case 1 (9)	53 yo	M	BC	None	Not described	Aortic ulcer	Surgical thrombectomy	Warfarin
Case 2 (10)	70 yo	M	GC	None	Protein C deficiency	Not described	Heparin/Warfarin	None
Present case	59 yo	F	SCLC	IS	None	Aortic calcification	Heparin	Aspirin

yo: years old, M: male, F: female, BC: bladder carcinoma, GC: gastric carcinoma, SCLC: small cell lung carcinoma, IS: ischemic stroke

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