Histological Examination of Thrombi in Patients with Cerebral Infarction in Embolic Stroke of Undetermined Source

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Objective: We pathologically examined thrombi collected by mechanical thrombectomy in Embolic Stroke of Undetermined Source (ESUS).

Methods: We examined the thrombi of acute ischemic stroke patients who underwent mechanical thrombectomy from January 2017 to June 2018. We histopathologically investigated the thrombi in ESUS patients, and performed a comparison with the thrombi of cardioembolic stroke.

Results: Mechanical thrombectomy was performed in 35 patients, and the thrombus were obtained from five patients diagnosed as ESUS.

The thrombus in one patient consisted of neutrophils and nuclear crush cells not only the red blood cells, and another one was included atheroma which was different from the typical clot in one patient. In the 25 cardioembolic stroke patients in this study, the thrombi were all constructed of fibrin, red blood cells, and platelets.

Conclusion: In this pathological study, a difference was recognized in the clot components of ESUS. The results suggest that a pathological examination of thrombi obtained by mechanical thrombectomy is useful because there is a possibility that we can recognize the etiology of ESUS, and choose the best treatment for prevention of recurrence of stroke.

Keywords ▶ embolic stroke of undetermined source, mechanical thrombectomy, clot pathology, ischemic stroke

Introduction

Recently, the treatment of acute cerebral infarction has changed. In particular, Japanese guidelines strongly recommended that mechanical thrombectomy should be performed in patients with acute-phase cerebral infarction based on the

results of five randomized, controlled trials,^{1–5)} which were reported in 2015 and an integrated analysis of these trials.⁶⁾ As a result, currently, mechanical thrombectomy is also positively performed in Japan.

When cerebral infarction occurs, various detailed examinations are conducted to prevent its recurrence, but its etiology is unclear in many cases⁷⁾; the condition is evaluated as cryptogenic stroke. Based on the assumption that a primary etiological factor for cryptogenic stroke may be cerebral embolism derived from an undetected source-of-embolism disease, a disease entity of “embolic stroke of undetermined source (ESUS)”⁷⁾ was proposed by a special working group in 2014. Even in patients whom thrombus retrieval was achieved by mechanical thrombectomy, leading to recanalization is suggested embolic-mechanism-mediated cerebral infarction, but the etiology is unclear despite various examinations in some patients, as described above, and the condition is also evaluated as ESUS.

Currently, retrieved thrombi are pathologically investigated. Several studies indicated that thrombi in patients with cryptogenic cerebral infarction often resembled the pathology of cardiogenic thrombi,^{8–10)} and that histological

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findings differed among mechanisms involved in thrombus formation, suggesting the possibility of clarifying the pathogenesis of cerebral infarction based on thrombi. However, in Japan, few studies have examined thrombi in ESUS patients, and no study has investigated subsequent treatment methods. In this study, we performed mechanical thrombectomy for acute cerebral infarction, and pathologically examined specimens from patients in whom the source of embolism was unclear based on the results of various examinations. Furthermore, we compared these specimens with thrombi in patients with cardiogenic cerebral embolism, and reviewed the pathogenesis and methods to prevent recurrence.

Materials and Methods

The subjects were patients who had undergone revascularization with a catheter for acute cerebral infarction between January 2017 and June 2018. Of these, we retrospectively investigated the age, sex, symptoms at the time of onset, site of occlusion, treatment, devices, and histology of thrombi in those in whom thrombi could be collected, suggesting the involvement of an embolic mechanism in the onset of cerebral infarction, and examinations for searching for the source of embolism during admission did not reveal any source of embolism. Thrombi that had been collected during endovascular treatment were histopathologically examined. Hematoxylin–eosin (HE) staining was conducted. When necessary, Elastica-Masson staining was additionally performed, and specimens were examined under a microscope. We also histopathologically examined thrombi using the same procedure in patients with cardiogenic cerebral embolism in whom atrial fibrillation was detected during admission, and compared components between these specimens and those from patients in whom the source of embolism was unclear.

As examinations during admission, blood collection, electrocardiography, chest X-ray, Holter's electrocardiography, left/right shunt tests (Bubble study), cervical vascular ultrasonography, transthoracic echocardiography, transeophageal echocardiography, lower limb venous ultrasonography, and cephalic magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) were conducted to examine the source of embolism.

Revascularization therapy was performed in accordance with the Japanese Guidelines for the Management of Stroke 2015 (addendum in 2017), Guidelines for the optimal use of devices for percutaneous transluminal cerebral thrombectomy, 2nd version (April 2015) (from January 2017 until

February 2018), and Guidelines for the optimal use of devices for percutaneous transluminal cerebral thrombectomy, 3rd version (March 2018) (from March 2018 until June 2018). Furthermore, intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) was selected as a first-choice procedure in patients for whom it could be indicated. In these patients, mechanical thrombectomy was performed after intravenous thrombolysis with rt-PA. In those in whom intravenous thrombolysis with rt-PA was not selected, mechanical thrombectomy alone was conducted. Concerning treatment methods, the femoral artery was punctured under local anesthesia, and 3000 to 5000 units of heparin were intra-arterially injected after sheath insertion. As a guiding catheter, a 9Fr OPTIMO (Tokai Medical, Aichi, Japan) was used. For recanalization, treatment with a stent retriever for thrombectomy alone, a direct aspiration first pass technique (ADAPT)^{11,12)} with a suction-type device for thrombectomy alone, or treatment with both stent retriever and suction-type device for thrombectomy was adopted based on the surgeon's evaluation. As devices for thrombectomy, a Trevo XP (Stryker Neurovascular, Fremont, CA, USA), Solitaire 2 (Medtronic, Minneapolis, MN, USA), and Penumbra system (Penumbra, Alameda, CA, USA) were used. When intraoperative resting could not be maintained, the intravenous injection of diazepam or continuous intravenous injection of propofol or dexmedetomidine was conducted at an appropriate time.

Recanalization was evaluated using the modified Thrombolysis In Cerebral Infarction (TICI) grade. TICI 2b or higher patients were regarded as achieving effective recanalization.¹³⁾

Results

In 35 patients, revascularization therapy was performed during the study period. In 26 of these, thrombi were retrieved. In 5 of the 26 patients, the involvement of an embolic mechanism in the onset of cerebral infarction was suggested, and examinations for searching for the source of embolism during admission did not reveal any source of embolism. Furthermore, 25 of the 35 patients had cardiogenic cerebral embolism. In 19 of these, thrombi could be retrieved. Revascularization therapy was also performed in five patients with atherothrombotic brain infarction. In two of these, a small volume of thrombi were observed. The volume of thrombi that could be retrieved in the patients with atherothrombotic brain infarction was extremely small, and pathological examination could not be conducted.

Table 1 Background factors

Case	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	68	54	73	55	49
Sex	Male	Male	Male	Male	Female
Risk factor	HT, SM	HT, DL	HT, DL, SM	DL, SM	HT, DL
NIHSS on arrival	24	17	16	30	25
Site of occlusion	Left middle cerebral artery	Left middle cerebral artery	Left middle cerebral artery	Left middle cerebral artery	Left internal carotid artery
Acute-phase treatment	Mechanical thrombectomy	rt-PA + mechanical thrombectomy	rt-PA + mechanical thrombectomy	Mechanical thrombectomy	rt-PA + mechanical thrombectomy
Device	Penumbra 5MAX ACE	Solitaire 6 × 30 mm + Penumbra 5MAX ACE	Trevo 3 × 20 mm + Penumbra 5MAX ACE	Trevo 4 × 20 mm + Penumbra 5MAX ACE	Penumbra 5MAX ACE
TICI	3	2b	3	2b	2b
OTR	363 min	145 min	280 min	492 min	194 min

AL: alcohol; DL: dyslipidemia; HT: hypertension; NIHSS: National Institutes of Health Stroke Scale; OTR: onset to recanalization; rt-PA: recombinant tissue plasminogen activator; SM: smoking; TICI: thrombolysis in cerebral infarction

Table 2 Histology of retrieved thrombus-like embolites, Post-therapy

	Case 1	Case 2	Case 3	Case 4	Case 5	Cardiogenic cerebral embolism
Histology of thrombus-like embolites	The thrombus consisted of a dense fibrin area containing neutrophils and nuclear debris and an erythrocyte area	The thrombus consisted of fibrin, erythrocytes, platelets, and a small amount of inflammatory cells. The contents of atheroma were not contained	A portion of the arterial intima and media was identified. In the arterial wall, atheroma containing foamy histiocytes and cholesterol crystals was observed	The thrombus consisted of fibrin, erythrocytes, platelets, and a small amount of inflammatory cells. The contents of atheroma were not contained	The thrombus consisted of fibrin, erythrocytes, platelets, and a small amount of inflammatory cells. The contents of atheroma were not contained	The thrombus consisted of fibrin, erythrocytes, platelets, and a small amount of inflammatory cells. The contents of atheroma were not contained
Post-therapy	Warfarin	Warfarin	Aspirin	Warfarin	Warfarin	DOAC/warfarin

DOAC: direct oral anticoagulants

Fig. 1 A representative case of ESUS (**Tables 1** and **2**, Case 3). A 73-year-old male. Right hemiplegia and aphasia suddenly occurred, and he was brought to our hospital by ambulance. Brain MRI revealed occlusion of the left middle cerebral artery. The interval from onset until arrival was 1 hour. Intravenous thrombolysis with rt-PA and mechanical thrombectomy were performed. **(A)** MRA. The visualization of the left M2 artery was reduced (white arrow head). **(B)** Angiography. A frontal view. The visualization of the distal left MCA was reduced (white arrow head). **(C)** LAO50°, CRA6°. There was a defect of contrast enhancement at the M2 superior branch (white arrow head). **(D)** Macroscopic findings of a retrieved thrombus. The thrombus was white and hard. **(E and F)** Histology of a retrieved thrombus. The thrombus was evaluated as a portion of the intima and media of the arterial wall. In the arterial wall, atherosclerosis involving cholesterol cleft (red arrow head) was observed (**E**: HE staining, **F**: Elastica-Masson staining, scale bar: 200 μ m). ESUS: Embolic Stroke of Undetermined Source; HE: hematoxylin–eosin; MCA: middle cerebral artery; MRA: magnetic resonance angiography; MRI: magnetic resonance imaging; rt-PA: recombinant tissue plasminogen activator

The details of each patient are summarized in **Table 1**. The median age was 55 years. The five patients consisted of four males and one female. Hypertension, dyslipidemia, and alcohol consumption were noted in four patients. Three patients had a history of smoking. No patient had diabetes mellitus. These patients consulted our hospital with right hemiplegia and aphasia. The median National Institutes of Health Stroke Scale (NIHSS) score was 24. The sites of occlusion consisted of the middle cerebral artery in four patients and internal carotid artery in one patient. Concerning treatment, combination therapy with rt-PA was performed in two patients, and thrombectomy alone in three patients. Treatment with ADAPT was selected in two patients, and a stent retriever device for thrombectomy was combined with a suction-type device in three patients. Effective recanalization was achieved in all patients. The TICI grade was evaluated as three in two patients and 2b in three patients. The mean onset-to-recanalization (OTR) time was

295 minutes in the ESUS patients. Furthermore, it was 371 minutes in the patients with cardiogenic cerebral embolism. The characteristics of the components of each thrombus are presented in **Table 2**. In Case 1, cerebral infarction occurred the day after surgery for lung cancer. Pathologically, the thrombus involved an area consisting of erythrocytes and another area consisting of neutrophils/nuclear debris. In this patient, various detailed examinations for clarifying the source of embolism did not reveal any source of embolism. Furthermore, contrast-enhanced computed tomography (CT) did not show any thrombus formation. In Case 3, right hemiplegia and aphasia were observed right after waking up, and the patient was brought to our hospital by ambulance. Pathologically, a white substance was collected (**Fig. 1D**). Histologically, it was evaluated as a portion of the tunica intima and media of a muscular artery including atherosclerosis (**Fig. 1E and 1F**). Furthermore, there was no stenosis of the middle cerebral artery after recanalization.

Fig. 2 A representative case of ESUS (Tables 1 and 2, Case 2). A 54-year-old male. Right hemiplegia suddenly appeared at work, and he was brought to our hospital by ambulance. To treat occlusion of the left middle cerebral artery, mechanical thrombectomy was performed in addition to intravenous thrombolysis with rt-PA. After discharge, an insertable cardiac monitor was inserted, and detailed examination has been continuously conducted at the outpatient clinic. (A) Angiography. Occlusion of the left middle cerebral artery (white arrow head). (B) Recanalization of the left middle cerebral artery was achieved. (C) Macroscopic findings of a retrieved thrombus. The thrombus was dark red (D and E). Histology of a retrieved thrombus. The thrombus consisted of fibrin, erythrocytes, platelets, and a small amount of inflammatory cells, and the contents of atheroma were not contained (HE staining, scale bar: 200 μ m (D), scale bar: 50 μ m (E)). (F) Chest X-ray after the insertion of an implantation-type electrocardiograph. ESUS: Embolic Stroke of Undetermined Source; HE: hematoxylin–eosin; rt-PA: recombinant tissue plasminogen activator

Examinations during admission, including aorta to carotid artery assessment and other examinations, did not reveal any significant lesion as the source of embolism. Concerning the remaining three patients, right hemiplegia and aphasia suddenly occurred at work in Case 2. In Case 4, right hemiplegia and aphasia were noted on waking up after a nap. In Case 5, right hemiplegia and aphasia suddenly occurred at home. In these patients, the thrombi consisted of fibrin, erythrocytes, and platelets; the contents of atheroma were not contained (Fig. 2D and 2E). In one of these, an implantation-type electrocardiograph had been inserted. In this patient, there has been no atrial fibrillation during the 1-year and 6-month follow-up. In the above five patients, there has been no recurrence, with a follow-up of 1 year to 1 year and 7 months.

In all 25 patients with cardiogenic cerebral embolism, atrial fibrillation was confirmed during admission. The thrombi consisted of fibrin, erythrocytes, and platelets; the contents of atheroma were not contained (Fig. 3C).

Discussion

If early vascular recanalization is achieved by mechanical thrombectomy, an embolic mechanism may be considered in the onset of cerebral infarction. However, the source of embolism is not clarified during admission, leading to a diagnosis of ESUS in many cases. In this study, the source of embolism was unclear in approximately 14.3% (5/35) of the subjects. This percentage is similar to that previously reported.¹⁴⁾

It is important to select antithrombotic drugs for the prevention of recurrence in patients with cerebral infarction, but randomized trials regarding recurrent stroke prevention involving patients with cryptogenic cerebral infarction, including the NAVIGATE ESUS trial^{15)/subgroup analysis,¹⁶⁾ RE-SPECT ESUS trial,¹⁷⁾ and subgroup analysis from the WARSS trial,¹⁸⁾ did not suggest recurrent-stroke-preventing treatment to be positively recommended for patients with cryptogenic cerebral infarction or ESUS. This is because the source of embolism varies.⁷⁾ Therefore, currently, the}

Fig. 3 A representative case of cardiogenic cerebral embolism (**Table 2**). A 49-year-old female. She suddenly fell down at home, and was brought to our hospital by ambulance. MRA revealed occlusion of the left middle and posterior cerebral arteries. Mechanical thrombectomy was performed. Electrocardiography on arrival showed atrial fibrillation. (**A**) Angiography showed occlusion of the left middle cerebral and posterior communicating (fetal type) arteries (white arrow head). (**B**) Recanalization was achieved. (**C** and **D**) Histology of a retrieved thrombus. The thrombus consisted of fibrin, erythrocytes, platelets, and a small amount of inflammatory cells, and the contents of atheroma were not contained (HE staining, scale bar: 500 μ m (**C**), scale bar: 200 μ m (**D**)). HE: hematoxylin–eosin; MRA: magnetic resonance angiography

source of embolism should be identified, if possible, when selecting effective recurrence-preventing drugs in patients with cryptogenic cerebral infarction or ESUS.

Recent studies indicated that the thrombus fibrin/erythrocyte and platelet/erythrocyte ratios in patients with cardiogenic cerebral embolism were higher than in those with non-cardiogenic cerebral embolism,¹⁹ and that the histology of thrombi in many patients with cryptogenic cerebral infarction resembled that of cardiogenic thrombi.^{8–10} As described above, several studies reported pathological findings of retrieved thrombi, and, in this study, we examined recurrence

prevention by antithrombotic drug therapy in reference to the pathological results of retrieved thrombi in patients diagnosed with ESUS through sufficient examinations.

Case 1 was a non-typical case. Our group published a case report.²⁰ In this patient, cerebral infarction occurred the day after surgery for lung cancer, suggesting embolism related to a thrombus in the resected margin of the pulmonary vein.²⁰ The incidence of cerebral infarction after surgery for lung cancer is approximately 0.3%, but this has been reported as a serious complication.²¹ After lobectomy, the resected margins of the pulmonary vein remain, and

intra-margin thrombus formation may cause cerebral infarction.²²⁾ In addition to blood flow congestion in the resected margin of the pulmonary vein, surgical-invasiveness-related inflammation at the margin may be involved in thrombus formation in a venous margin.²⁰⁾ In this patient, neither subsequent contrast-enhanced CT nor various examinations revealed any thrombus, and it is impossible to clarify the source of embolism. However, a portion of the retrieved thrombi consisted of neutrophils and dense fibrin containing a large amount of nuclear debris, reflecting topical inflammation at the margin.²⁰⁾ As blood flow congestion in a venous margin may be involved in thrombus formation, we selected Warfarin, considering that anticoagulant therapy is appropriate for the prevention of recurrence. In Case 3, histological findings included a portion of the tunica intima and media of a muscular artery including atheroma, but not a thrombus. In the retrieved arterial intima, atheroma was detected, suggesting the involvement of an arteriosclerotic mechanism in the onset of cerebral infarction. As etiological factors, an aortic lesion and a lesion at the origin of the common carotid artery were suspected, but there was no source of embolism. This mechanism is suggested the involvement of arteriosclerosis. Therefore, to prevent recurrence, we introduced aspirin, considering the risk of hemorrhage and usefulness of antiplatelet therapy in comparison with anticoagulant therapy, as described in the guidelines.

In the other three patients, Warfarin was selected to prevent recurrence based on the following results: although neither the NAVIGATE ESUS¹⁵⁾ nor RE-SPECT ESUS¹⁷⁾ trials showed the usefulness of anticoagulant therapy in comparison with aspirin in patients with embolic cerebral infarction, a subgroup analysis from the NAVIGATE ESUS trial (NAVIGATE ESUS patent foramen ovale) indicated that anticoagulant therapy decreased the risk of recurrent ischemic stroke in patients with Patent Foramen Oval (PFO),¹⁶⁾ and a WARSS subgroup analysis¹⁸⁾ also demonstrated that Warfarin more markedly prevented recurrent cerebral infarction compared with aspirin. According to a study, paroxysmal atrial fibrillation was considered to be an etiological factor in $\geq 40\%$ of patients with ESUS.²³⁾ Therefore, considering the possibility that paroxysmal atrial fibrillation may be detected in the future, an insertable cardiac monitor was inserted in one patient, excluding two who were referred to a rehabilitation hospital. An etiological factor has been continuously investigated at the outpatient clinic. However, there has been no atrial fibrillation during the 1-year and 6-month follow-up after insertion, and the source of embolism has not been clarified. In the

future, further long-term follow-up may be necessary, but there has been no recurrence in the above five patients, with a follow-up of 1 year to 1 year and 7 months. This study suggests that the mechanism of thrombus formation can be predicted in some patients with ESUS by histologically examining thrombi extirpated by mechanical thrombectomy. In the future, further long-term follow-up involving a larger number of patients may be necessary, but histopathological examination of retrieved thrombi may contribute to the selection of the most appropriate recurrence-preventing treatment in addition to the more accurate assessment of the pathogenesis; this procedure may be useful.

This study has some limitations. Initially, in this study, the number of patients was small. In both ESUS and cardiogenic cerebral embolism patients, thrombi should be further analyzed. Second, the follow-up period was not established, and there are few data regarding the prevention of recurrence. In the future, a larger number of patients must be followed-up over a long period. Lastly, the rates of components were quantitatively compared using image-analyzing software in the articles described above, whereas quantitative assessment was not performed in this study. Furthermore, in this study, only one sample slice was evaluated, and its histology may not reflect the characteristics of all thrombi.

Conclusion

We histopathologically investigated thrombi in five patients with ESUS. The mechanism of thrombus formation may be predicted in some patients with ESUS. Histopathological examination of retrieved thrombi may contribute to the selection of the most appropriate recurrence-preventing treatment in addition to the more accurate assessment of the pathogenesis; this procedure may be useful. In the future, a large-scale study involving a larger number of patients should be conducted.

Disclosure Statement

As the author has completed self-reporting of COI to the Japanese Society for Neuroendovascular Therapy, there is no COI to be disclosed regarding the publication of this article. There is also no COI for the coauthors.

References

- 1) Berkhemer OA, Fransen PS, Beumer D, et al: A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372: 11–20.

- 2) Goyal M, Demchuk AM, Menon BK, et al: Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; 372: 1019–1030.
- 3) Campbell BC, Mitchell PJ, Kleinig TJ, et al: Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015; 372: 1009–1018.
- 4) Saver JL, Jahan R, Levy EI, et al: Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012; 380: 1241–1249.
- 5) Jovin TG, Chamorro A, Cobo E, et al: Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015; 372: 2296–2306.
- 6) Goyal M, Menon BK, van Zwam WH, et al: Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387: 1723–1731.
- 7) Hart RG, Diener HC, Coutts SB, et al: Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; 13: 429–438.
- 8) Boeckh-Behrens T, Schubert M, Förchler A, et al: The impact of histological clot composition in embolic stroke. *Clin Neuroradiol* 2016; 26: 189–197.
- 9) Sporns PB, Hanning U, Schwindt W, et al: Ischemic stroke: what does the histological composition tell us about the origin of the thrombus? *Stroke* 2017; 48: 2206–2210.
- 10) Maekawa K, Shibata M, Nakajima H, et al: Erythrocyte-rich thrombus is associated with reduced number of maneuvers and procedure time in patients with acute ischemic stroke undergoing mechanical thrombectomy. *Cerebrovasc Dis Extra* 2018; 8: 39–49.
- 11) Turk AS, Frei D, Fiorella D, et al: ADAPT FAST study: a direct aspiration first pass technique for acute stroke thrombectomy. *J Neurointerv Surg* 2014; 6: 260–264.
- 12) Lapergue B, Blanc B, Gory B, et al: Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion. *JAMA* 2017; 318: 443–452.
- 13) Noser EA, Shaltoni HM, Hall CE, et al: Aggressive mechanical clot disruption: a safe adjunct to thrombolytic therapy in acute stroke? *Stroke* 2005; 36: 292–296.
- 14) Perera KS, Vanassche T, Bosch J, et al: Embolic strokes of undetermined source: prevalence and patient features in the ESUS Global Registry. *Int J Stroke* 2016; 11: 526–533.
- 15) Hart RG, Sharma M, Mundl H, et al: Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018; 378: 2191–2201.
- 16) Kasner SE, Swaminathan B, Lavados P, et al: Rivaroxaban or aspirin for patent foramen ovale and embolic stroke of undetermined source: a prespecified subgroup analysis from the NAVIGATE ESUS trial. *Lancet Neurol* 2018; 17: 1053–1060.
- 17) Diener HC, Easton JD, Granger CB, et al: RE-SPECT ESUS investigators. Design of randomized, double-blind, evaluation in secondary stroke prevention comparing the Efficacy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic stroke of undetermined source (RE-SPECT ESUS). *Int J Stroke* 2015; 10: 1309–1312.
- 18) Sacco RL, Prabhakaran S, Thompson JL, et al: Comparison of warfarin versus aspirin for the prevention of recurrent stroke or death: subgroup analyses from the Warfarin-aspirin recurrent stroke study. *Cerebrovasc Dis* 2006; 22: 4–12.
- 19) Boeckh-Behrens T, Kleine JF, Zimmer C, et al: Thrombus histology suggests cardioembolic cause in cryptogenic stroke. *Stroke* 2016; 47: 1864–1871.
- 20) Usui G, Takayama Y, Hashimoto H, et al: Cerebral embolism caused by thrombus in the pulmonary vein stump after left lower lobectomy: a case report and literature review. *Intern Med* 2019; 58: 1349–1354.
- 21) Yamamoto T, Yagi S, Uryuhara K, et al: Clinical factors that affect the outcomes after anatomical versus non-anatomical resection for hepatocellular carcinoma. *Surg Today* 2017; 47: 193–201.
- 22) Ohtaka K, Hida Y, Kaga K, et al: Thrombosis in the pulmonary vein stump after left upper lobectomy as a possible cause of cerebral infarction. *Ann Thorac Surg* 2013; 95: 1924–1928.
- 23) Ntaios G, Papavasileiou V, Milionis H, et al: Embolic strokes of undetermined source in the Athens stroke registry: a descriptive analysis. *Stroke* 2015; 46: 176–181.