Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1962-18
Intern Med 58: 1349-1354, 2019
http://internmed.jp

【 CASE REPORT 】

Cerebral Embolism Caused by Thrombus in the Pulmonary Vein Stump after Left Lower Lobectomy: A Case Report and Literature Review

Genki Usui[1,2], Yohei Takayama[1], Hirotsugu Hashimoto[2], Takehiro Katano[1], Masahiro Yanagiya[3], Masashi Kusakabe[4], Tamaki Miura[2], Jun Matsumoto[3], Hajime Horiuchi[2] and Seiji Okubo[1]

Abstract:
Cerebral embolism after left upper lobectomy caused by a thrombus in the pulmonary vein stump (PVS) is a serious complication. However, it is unclear if cerebral embolism can develop after other types of lobectomy. We present a case of a 68-year-old man with cerebral embolism after left lower lobectomy with a longer PVS than normal. There were no clinically suspected sources for the thrombus except for the PVS. This thrombus seemed to have formed in the PVS. The endovascularly removed thrombus contained scattered nuclear debris around neutrophils, suggesting a physiological response caused by tissue injury.

Key words: stroke, endovascular thrombectomy, lung cancer

(Intern Med 58: 1349-1354, 2019)
(DOI: 10.2169/internalmedicine.1962-18)

Introduction

Cerebral embolism after lung cancer surgery is a rare and serious complication, developing in approximately 0.4% of cases (1). However, it is a serious complication. Cerebral embolism develops after left upper lobectomy (LUL), which consistently leaves a longer pulmonary vein stump (PVS) than other types of lobectomy. It has been reported that a thrombus in the vein stump can cause cerebral embolism (1, 2). In contrast, cerebral embolism caused by a thrombus in the vein stump after left lower lobectomy (LLL) has not been reported to our knowledge. Although some theories about the mechanism of thrombus formation have been proposed, this has not been investigated in detail.

We herein report the case of a patient with cerebral embolism after LLL with a longer PVS than normal.

Case Report

A 68-year-old man was referred to the Department of General Thoracic Surgery of our hospital because of an abnormal shadow on chest computed tomography (CT). His medical history included hypertension and end-stage renal failure owing to hypertensive nephrosclerosis that had been treated with hemodialysis. He had a smoking history of 20 pack-years. He had no history of cerebrovascular disease, atrial fibrillation (AF), or heart disease. Chest CT to investigate the cause of his chronic anemia incidentally detected two part-solid ground-glass nodules (13 mm in S^8 and 5 mm in S^9). The ground-glass nodules grew slightly during the follow-up period, which led to a diagnosis of lung cancer [cT1bN0M0-stage IA as defined by the 7th Edition of TNM classification (TNM7) of lung cancer] (3). Video-assisted thoracoscopic LLL was performed three years and two months after his first visit. The pathological diagnosis of

[1]Department of Cerebrovascular Medicine, NTT Medical Center Tokyo, Japan, [2]Department of Diagnostic Pathology, NTT Medical Center Tokyo, Japan, [3]Department of General Thoracic Surgery, NTT Medical Center Tokyo, Japan and [4]Department of Radiology, NTT Medical Center Tokyo, Japan
Received: August 16, 2018; Accepted: October 15, 2018; Advance Publication by J-STAGE: December 18, 2018
Correspondence to Dr. Genki Usui, gusui-tky@umin.ac.jp

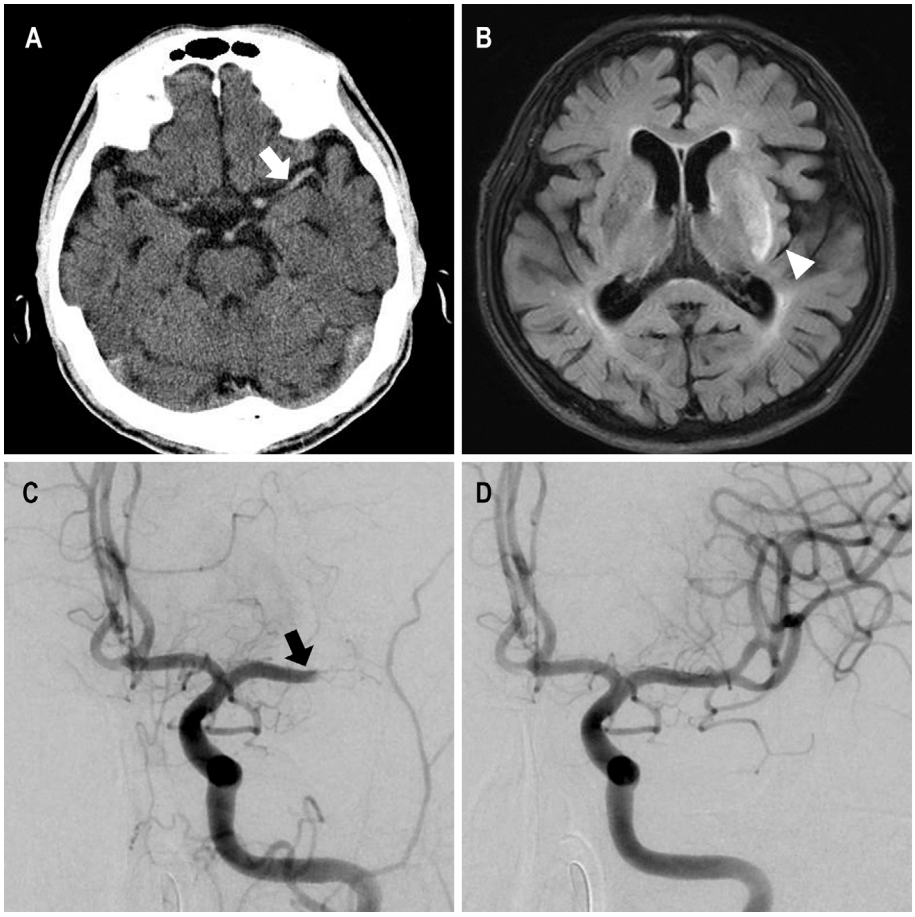

Figure 1. **Cerebral embolism in the region of the left middle cerebral artery. (A) Head computed tomography displayed a hyperdense middle cerebral artery sign (arrow). (B) Magnetic resonance imaging displayed a high-signal-intensity area in the left basal ganglia on fluid-attenuated inversion recovery on the day after the endovascular removal of the thrombus (arrowhead). (C) Cerebral angiography displayed a left middle cerebral artery that was interrupted in the middle of the horizontal part, whereas the distal artery was not displayed (arrow). (D) Cerebral angiography displayed the entire left middle cerebral artery after endovascular removal of the thrombus by the Penumbra System.**

both tumors was lepidic adenocarcinoma (pT1bN0M0-stage IA as defined by the TNM7 of lung cancer) (3).

At 27 hours after the surgery, the patient was referred to the Department of Cerebrovascular Medicine with consciousness disturbance [Glasgow Coma Scale, 8 points (E2V 2M4)], conjugate deviation of the eyes to the left, right complete hemiplegia, and mixed aphasia. The patient's score on the National Institutes of Health Stroke Scale (NIHSS) was 24. Blood tests showed that his brain natriuretic peptide level was 124.6 pg/mL (normal, <18.4 pg/mL), and the D-dimer level was 2.6 μg/mL (normal, <1.0 pg/mL). Electrocardiography displayed a sinus rhythm. Carotid ultrasonography displayed no meaningful stenosis in the bilateral carotid artery. Head CT displayed a hyperdense middle cerebral artery (MCA) sign, which suggested acute middle cerebral artery infarction (Fig. 1A). Because he was a postoperative patient, tissue plasminogen activator was not administered. On cerebral angiography, the left MCA was found to be interrupted in the middle of the horizontal region, and the distal artery was not visible (Fig. 1C). The thrombus was endovascularly removed using the Penumbra System, which is a mechanical thrombectomy device, and successful recanalization (thrombolysis on the cerebral infarction scale, 2b) was achieved (Fig. 1D).

The endovascularly removed thrombus was subjected to a histopathological analysis. The thrombus consisted of two parts: the first part contained many neutrophils trapped within a dense laminar fibrin network, together with red blood cells (RBCs) and platelets (Fig. 2A and B). Nuclear debris was scattered around the neutrophils (Fig. 2C). The second one contained many RBCs entrapped within a subtle mesh-like fibrin network (Fig. 2D). Platelets were also trapped within the fibrin network, with fewer neutrophils. The thrombus structure was more similar to that of a freshly formed thrombus than an organized longstanding thrombus. There were no cholesterin clefts or foamy cells, suggesting that the thrombus had not been formed by atherosclerosis.

Electrocardiographic monitoring displayed no AF after

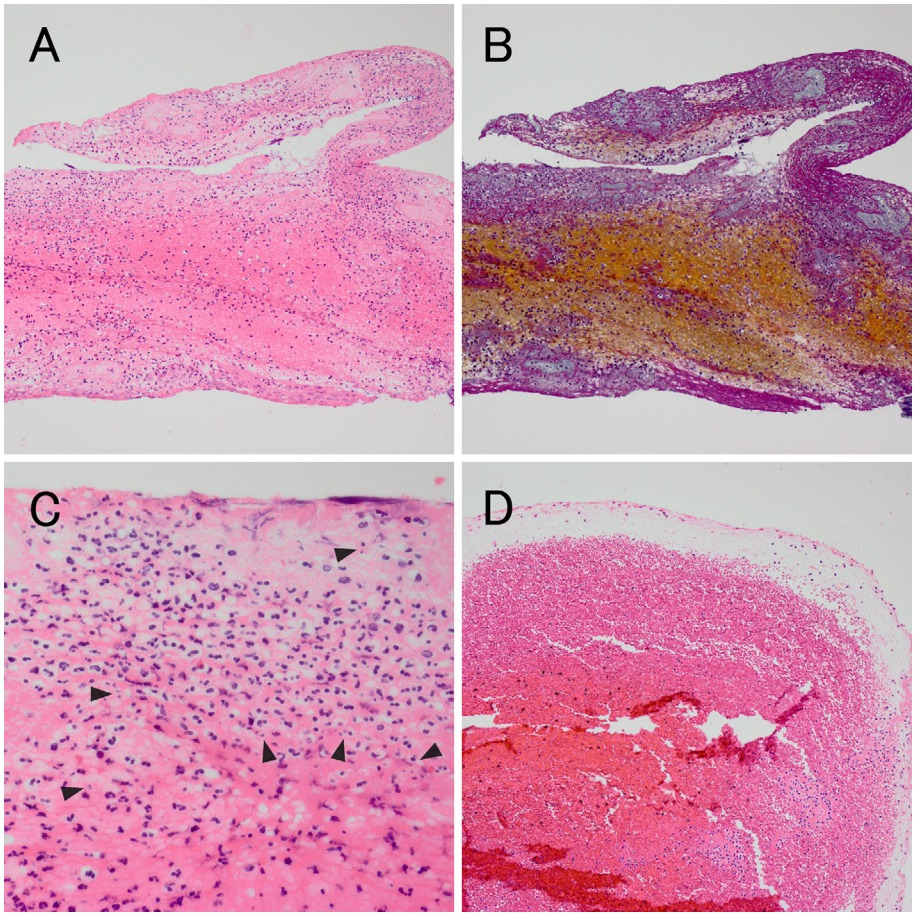

Figure 2. **Histopathology of the removed thrombus. (A) The first part of the thrombus contained neutrophils, platelets, and red blood cells within a dense laminar fibrin network. (B) Combined Verhoeff and Masson trichrome staining showed that the thrombus was not organized, and dense laminar fibrin was shown in reddish purple. (C) A higher-power field showed many neutrophils trapped within a fibrin network as well as many scattered nuclear debris (arrowheads), suggestive of a strong inflammatory response in this area. (D) The second part of the thrombus had many red blood cells together with platelets trapped within a subtle mesh-like fibrin network. Fewer neutrophils were observed in this component than in the first part of the thrombus, suggesting that this part of the thrombus had been formed by different mechanisms from the first part [original magnification ×100 (A, B, D); original magnification ×400 (C)].**

surgery, and transthoracic echocardiography, transesophageal echocardiography, and venous ultrasonography displayed no thrombus. Contrast-enhanced chest CT showed a left inferior pulmonary vein (LIPV) stump, with a length of 1.4 cm, in which no thrombus was found (Fig. 3). There were no other suspected sources; however, anticoagulant therapy with heparin was started owing to the possibility of a cerebral embolism. On the day after thrombus removal, the neurological function was dramatically improved (NIHSS score, 4 points). Magnetic resonance imaging displayed a high-signal intensity area in the left basal ganglion on fluid-attenuated inversion recovery (Fig. 1B) and no low-intensity area on T 2-star-weighted imaging. Magnetic resonance angiography demonstrated that the left MCA did not have any interruptions. Three days after thrombus removal, his NIHSS score was 0. The patient had no major complications, was discharged from our hospital, and continued taking warfarin (3 mg/day). The patient has since been followed up as an outpatient and has not experienced a recurrence of a cerebral embolism for three years and five months since the last episode.

Discussion

This is a rare case of cerebral embolism after lung cancer surgery. The following are the known causes of embolic stroke: cardiogenic, arteriogenic, paradoxical, and cancer-associated embolisms (4). In our present case, cerebral embolism was presumably caused by a thrombus in the PVS because there were no other suspected sources, and electrocardiographic monitoring detected no AF after surgery. Our case suggested that two factors contributed to thrombus formation in the PVS: length and inflammation.

Although eight cases of cerebral embolism caused by a

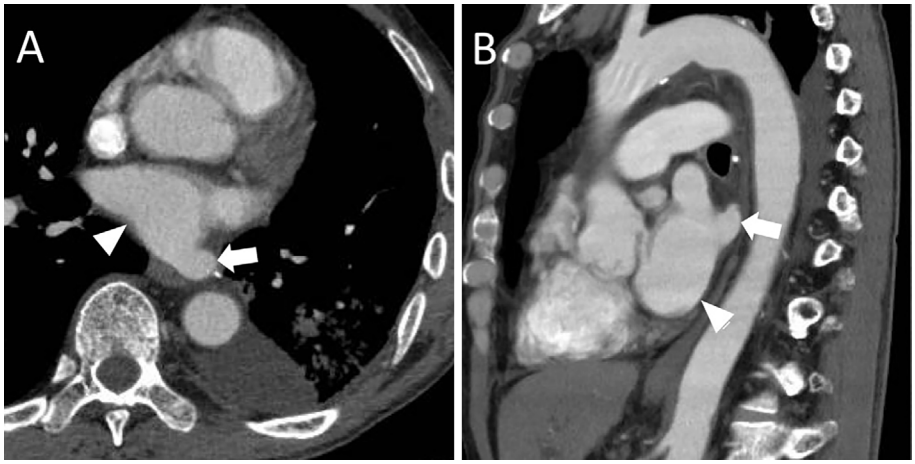

Figure 3. **Left inferior pulmonary vein stump after left lower lobectomy. (A, B) Contrast-enhanced chest computed tomography showed a left inferior pulmonary vein stump with a length of 1.4 cm (arrow). No thrombus remained in the left inferior pulmonary vein stump. The arrowhead indicates the right atrium.**

Table. **Summary of Patients with Cerebral Embolism Caused by a Thrombus in the Pulmonary Vein Stump after Lobectomy.**

Ref.	Age	Sex	Type of lobectomy	Postoperative period	Risk factors of cerebrovascular disease	Treatment
5	66	M	LUL	18 months	Smoking history, cancer*	Conservative therapy
6	70	M	LUL	7 years	HL, smoking history	Anticoagulation therapy
7	46	F	LUL	6 months	Not reported	Surgical removal of pulmonary vein thrombus, anticoagulation therapy
8	58	M	LUL	2 days	Smoking history	Endovascular removal of thrombus, anticoagulation therapy
1	70	M	LUL	1 day	HT, DM, HL	Anticoagulation therapy
1	68	M	LUL	9 days	HL	Not reported
1	55	M	LUL	3 days	None	Not reported
9	77	F	LUL	8 days	Not reported	Anticoagulation therapy
This study	68	M	LLL	1 day	HT, DM, CKD, smoking history	Endovascular removal of thrombus, anticoagulation therapy

(*) maxillary, oropharyngeal, tongue cancer.

M: male, F: female, LUL: left upper lobectomy, LLL: left lower lobectomy, HT: hypertension, DM: diabetes mellitus, HL: hyperlipidemia, CKD: chronic kidney disease

thrombus in the PVS have been reported to date (Table) (1, 5-9), all of these cases occurred after LUL. This is because LUL consistently leaves a longer PVS (median length of 1.7 cm) than other types of lobectomy, allowing blood congestion to occur easily (2). In contrast, the median length of the LIPV stump in LLL is 0.5 cm, and blood congestion is less likely to occur (2). In our case, the LIPV stump was 1.4 cm in length, which is longer than the median length and appears to have been one of the causes of thrombogenesis in this patient.

The dominant view is that blood congestion is the main cause of thrombogenesis (10, 11). Regarding AF, which causes thrombogenesis by blood congestion, it is widely known that the risk of thromboembolic complications is very low when cardioversion is performed without anticoagulants within 48 hours of AF onset (12). This means that a thrombus that causes embolic complications is seldom formed by only blood congestion within 48 hours of AF onset. Our patient developed a cerebral embolism 27 hours after lobectomy, and in some patients, cerebral embolisms have been reported to develop in the early postoperative period, which suggests that not only blood congestion but other factors may also contribute to thrombogenesis of the vein stump.

The pathological findings of the removed thrombus suggested that inflammation at the PVS also contributed to

thrombus formation. The first part of the removed intracerebrovascular thrombus contained many neutrophils trapped in a dense laminar fibrin network, together with RBCs and platelets. The thrombus consisted of fewer RBCs and more white blood cells than the typical thrombus (13-15). In this case, platelet aggregation and leukocyte recruitment at the thrombus suggested endothelial injury at the PVS. Thrombus formation was likely to be caused by the physiological response to tissue injury after surgery, and a recent study suggested that immune cells, such as neutrophils, play an important role in thrombus formation (16). The second part of the thrombus contained fewer white blood cells than the first part and included many RBCs and fibrins, which are typically seen in thrombi caused by blood congestion (13-15). This part of the thrombus is therefore likely to have been formed by blood congestion.

No method for preventing cerebral embolism after lobectomy has been established. We reported a case of thrombus reformation in the PVS after cerebral embolism after LUL for lung cancer. Thrombus reformation was seen even though the patient had already been treated with preventative antiplatelet therapy (17). Anticoagulation therapy should be considered in order to prevent thrombus formation in the PVS. However, as bleeding complications after lobectomies can be fatal, administering anticoagulation therapy to all patients after lobectomy for the prevention of cerebral embolism is controversial (1). Anticoagulation therapy should therefore be considered for only high-risk patients. These patients may be selected according to the $CHADS_2$/$CHADS_2$ VASc score (18, 19), which is a criterion for cardiogenic cerebral embolism. This score may also be used to predict the risk of cerebral embolism after lobectomy, as blood congestion is also associated with it.

The characteristics of PVS seem to be important for estimating the risk of cerebral embolism after lobectomy. As previous studies and our case suggested that a longer PVS may contribute to thrombus formation (2), anticoagulation therapy should be considered in patients with a longer PVS, not limited to LUL. In addition, the choice of operative procedure may also be important for estimating the risk of cerebral embolism after lobectomy. The inflammatory response to endothelial injury also seems to contribute to thrombus formation (11, 16). The degree of inflammation may be affected by the operative procedure, such as thoracotomy versus thoracoscopic surgery and automatic versus manual sutures. However, such factors have never been investigated thoroughly. Further studies are expected to address these issues.

In conclusion, this is the first case of a cerebral embolism presumably caused by a thrombus in the PVS after LLL for lung cancer. The thrombus might have been formed in the LIPV stump due to the relatively long PVS and tissue injury caused by surgery in the early postoperative period.

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

Acknowledgement

We thank Mr. Goichiro Yanagi, the clinical technologists, and the radiological technologists of NTT Medical Center Tokyo for their excellent technical assistance. We also would like to thank Dr. Helena Akiko Popiel, Dr. Ryuichiro Sasae.

References

1. Yamamoto T, Suzuki H, Nagato K, et al. Is left upper lobectomy for lung cancer a risk factor for cerebral infarction? Surg Today **46**: 780-784, 2016.

2. 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 **95**: 1924-1928, 2013.

3. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (Seventh) edition of the TNM Classification of Malignant Tumours. J Thorac Oncol **2**: 706-714, 2007.

4. Hart RG, Diener HC, Coutts SB, et al.; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol **13**: 429-438, 2014.

5. Ohtaka K, Hida Y, Kaga K, et al. Pulmonary vein thrombosis after video-assisted thoracoscopic left upper lobectomy. J Thorac Cardiovasc Surg **143**: e3-e5, 2012.

6. Gual-Capllonch F, Teis A, Palomeras E. Pulmonary vein spontaneous echocontrast and stroke after pulmonary lobectomy. J Clin Ultrasound **41**: 321-322, 2013.

7. Ohira S, Doi K, Okawa K, et al. Surgical removal of extensive left pulmonary vein stump thrombus after pulmonary lobectomy: a rare cause of acute cerebral embolism. Ann Thorac Surg **96**: e135-e136, 2013.

8. Ikeda H, Yamana N, Murata Y, et al. Thrombus removal by acute-phase endovascular reperfusion therapy to treat cerebral embolism caused by thrombus in the pulmonary vein stump after left upper pulmonary lobectomy: case report. NMC Case Rep J **2**: 26-30, 2014.

9. Nakano T, Inaba M, Kaneda H. Recurrent cerebral attack caused by thrombosis in the pulmonary vein stump in a patient with left upper lobectomy on anticoagulant therapy: case report and literature review. Surg Case Rep **3**: 101, 2017.

10. Ohtaka K, Hida Y, Kaga K, et al. Left upper lobectomy can be a risk factor for thrombosis in the pulmonary vein stump. J Cardiothorac Surg **9**: 5, 2014.

11. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet **373**: 155-166, 2009.

12. Nuotio I, Hartikainen JE, Grönberg T, et al. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. JAMA **312**: 647-649, 2014.

13. Boeckh-Behrens T, Schubert M, Förschler A, et al. The impact of histological clot composition in embolic stroke. Clin Neuroradiol **26**: 189-197, 2016.

14. Boeckh-Behrens T, Kleine JF, Zimmer C, et al. Thrombus histology suggests cardioembolic cause in cryptogenic stroke. Stroke **47**: 1864-1871, 2016.

15. Spornd PB, Hanning U, Schwindt W, et al. Ischemic stroke: what does the histological composition tell us about the origin of the thrombus? Stroke **48**: 2206-2210, 2017.

16. Pfeiler S, Stark K, Massberg S, et al. Propagation of thrombosis by neutrophils and extracellular nucleosome networks. Haematologica **102**: 206-213, 2017.

17. Usui G, Matsumoto J, Hashimoto H, et al. Thrombus reformation in the pulmonary vein stump confirmed 16 months after cerebral embolism on the day after left upper lobectomy for lung cancer. J

Stroke Cerebrovasc Dis **27**: e225-e227, 2018 (Epub ahead of print).

18. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA **285**: 2864-2870, 2001.

19. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. Chest **137**: 263-272, 2010.