

## Histological Examination of Trousseau Syndrome-Related Thrombus Retrieved Through Acute Endovascular Thrombectomy: Report of 2 Cases

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The mechanism of thrombus formation in Trousseau syndrome remains unclear. The purpose of this study was to investigate specific pathological findings of the thrombi in Trousseau syndrome. The authors report on 2 cases of thrombi in Trousseau syndrome from large cerebral vessels removed by endovascular therapy and compared with thrombi in atherosclerosis or cardiac embolism. The first patient, a 67-year-old man, was transferred to our hospital for sudden onset consciousness disturbance and tetraparesis. He had been diagnosed with stage IV lung cancer. The magnetic resonance (MR) angiography demonstrated basilar artery occlusion. An endovascular thrombectomy was performed. The second patient, an 84-year-old woman, was transferred to our hospital for sudden onset motor aphasia and right-sided motor weakness. She has a history of stage IV pancreatic body cancer. The MR angiography demonstrated left middle cerebral artery occlusion. An endovascular thrombectomy was performed for the floating thrombus. Macroscopic findings of retrieved thrombi were observed immediately after thrombectomy. The thrombi in Trousseau syndrome were white in color and solid against manual compression, whereas thrombi from other causes were red and fragile. In terms of microscopic findings, the thrombi in Trousseau syndrome mainly contained fibrin. On the other hand, thrombi associated with atherosclerosis or cardiac embolism had smaller area of fibrin with a considerable amount of red and white blood cells. The thrombi in Trousseau syndrome, which caused occlusion of large cerebral vessel, almost exclusively consisted of fibrin. **Key Words:** Thrombus—acute cerebral large vessel occlusion—Trousseau syndrome—histological examination. © 2016 National Stroke Association. Published by Elsevier Inc. All rights reserved.

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Received May 10, 2016; revision received July 13, 2016; accepted August 27, 2016.

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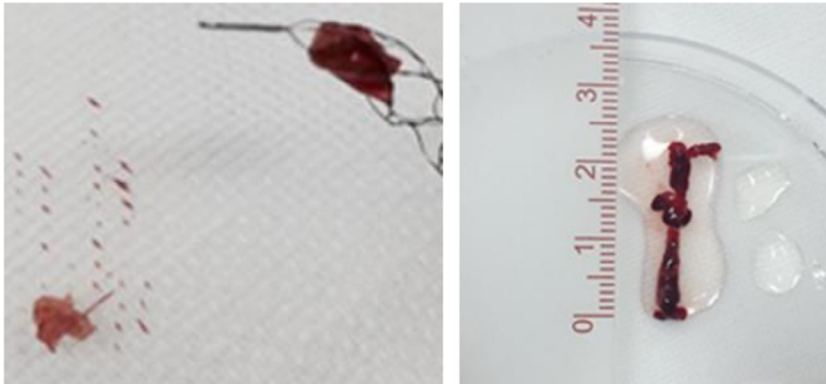
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<http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.041>

### Introduction

Trousseau syndrome is characterized as cerebral embolism due to hypercoagulation related to malignant tumors.<sup>1</sup> The mechanism of thrombus formation in Trousseau syndrome remains unclear, and thus there is no evidence for secondary prevention.

We retrieved 2 thrombi in 2 cases with acute cerebral large vessel occlusion related to Trousseau syndrome using neuroendovascular therapy, performed histological examination, and compared the thrombi with 7 from other



**Figure 1.** Macroscopic findings of the retrieved thrombi. (Left) The thrombus in Trousseau syndrome, retrieved from patient CASE 2, was white in color and solid. (Right) The thrombus of atherosclerotic brain infarction, retrieved from patient ATBI 3, was red in color and fragile.

causes (atherosclerotic thrombus [ATBI] = 4, cardiogenic embolism [CE] = 2, embolic stroke of undetermined source = 1), according to Trial of ORG 10172 in Acute Stroke Treatment classification.<sup>2</sup>

Tissue plasminogen activator (tPA) was administered to 4 of 9 patients. The thrombi were retrieved by stent retrievers in 8 cases and by an aspiration catheter in 1 case.

### Case Presentation

Case 1 is a 67-year-old man who was transferred to our hospital for sudden onset consciousness disturbance and tetraparesis. He had been diagnosed with stage IV lung cancer but had been doing well without any evidence of multiple organ failure or hemorrhagic complications. The laboratory data included platelet of  $9.3 \times 10^4/\mu\text{L}$ , D-dimer level of more than  $10.0 \mu\text{g}/\text{mL}$ , plasma fibrinogen of  $239.0 \text{ mg}/\text{dL}$ , fibrin degradation product of  $71.7 \mu\text{g}/\text{mL}$ , and prothrombin time of 15.2 seconds, suggesting that the patient did not present with clinically overt disseminated intravascular coagulation (DIC), assessed using International Society on Thrombosis and Haemostasis criteria.<sup>3</sup> The diffusion-weighted imaging of head magnetic resonance imaging (MRI) and MR angiography (MRA) demonstrated acute stage bilateral cerebellar infarction and basilar artery occlusion, respectively. Cardiac vegetation was not detected by transthoracic echocardiogram. Given lack of evidence for ATBI and CE, his embolism was categorized into Trousseau syndrome. tPA was not administered because of low platelet count. His thrombus in the basilar artery was retrieved by a stent retriever.

Case 2 is an 84-year-old woman who was transferred to our hospital for sudden onset motor aphasia and right-sided motor weakness. She has a history of stage IV pancreatic body cancer but had been doing well without any evidence of multiple organ failure or hemorrhagic complications. The laboratory data included platelet of  $16.3 \times 10^4/\mu\text{L}$ , D-dimer level of  $19.9 \mu\text{g}/\text{mL}$ , plasma fibrinogen of  $164.0 \text{ mg}/\text{dL}$ , fibrin degradation product of  $44.6 \mu\text{g}/\text{mL}$ , and prothrombin time of 15.2 seconds, sug-

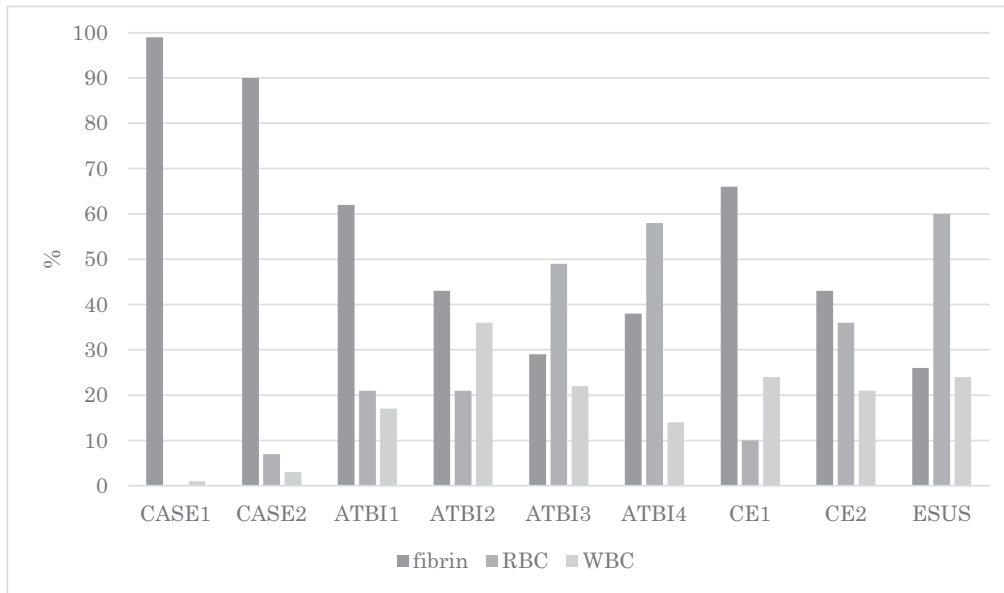
gesting that the patient did not present with clinically overt DIC, assessed using International Society on Thrombosis and Haemostasis criteria.<sup>3</sup> MRI and MRA demonstrated acute stage infarction of left corona radiata and left middle cerebral artery occlusion, respectively. Cardiac vegetation was not detected by transthoracic echocardiogram. She demonstrated drastic recovery temporarily after MRI so that tPA was not administered. A few hours later, her symptoms deteriorated again. Thrombectomy was performed by a stent retriever.

Macroscopic findings of retrieved thrombi were observed immediately after thrombectomy. The thrombi in Trousseau syndrome were white in color and solid against manual compression, whereas thrombi from other causes were red and fragile (Fig 1). In terms of microscopic findings, the proportion of the area of each hematological component in the thrombi is shown in Figure 2. The thrombi of Trousseau syndrome contained more than 90% fibrin. On the other hand, thrombi associated with ATBI, CE, or embolic stroke of undetermined source had smaller area of fibrin and a considerable amount of red and white blood cells. No tumor cells were found in the thrombi in Trousseau syndrome (Fig 3).

### Discussion

Trousseau syndrome was reported by Armand Trousseau in 1865 and is characterized by cerebral embolism caused by hypercoagulation due to malignant tumors. Although there are no defined criteria to differentiate Trousseau syndrome from other infarctions, Trousseau syndrome has been reported to be associated with extremely high level of plasma D-dimer level.<sup>4</sup>

The mechanism of thrombus formation in cerebral large arteries in Trousseau syndrome remains unclear. However, nonbacterial thrombotic endocarditis (NBTE) associated with hypercoagulation is most commonly accepted as an embolic source.<sup>5</sup> The cardiac vegetation formed in NBTE was reported to mainly consist of fibrin component and sparsely include leukocytes or erythrocytes,<sup>6</sup> which is similar to thrombi of DIC in microvessels.<sup>7</sup> In the present study, thrombi associated with Trousseau syndrome con-

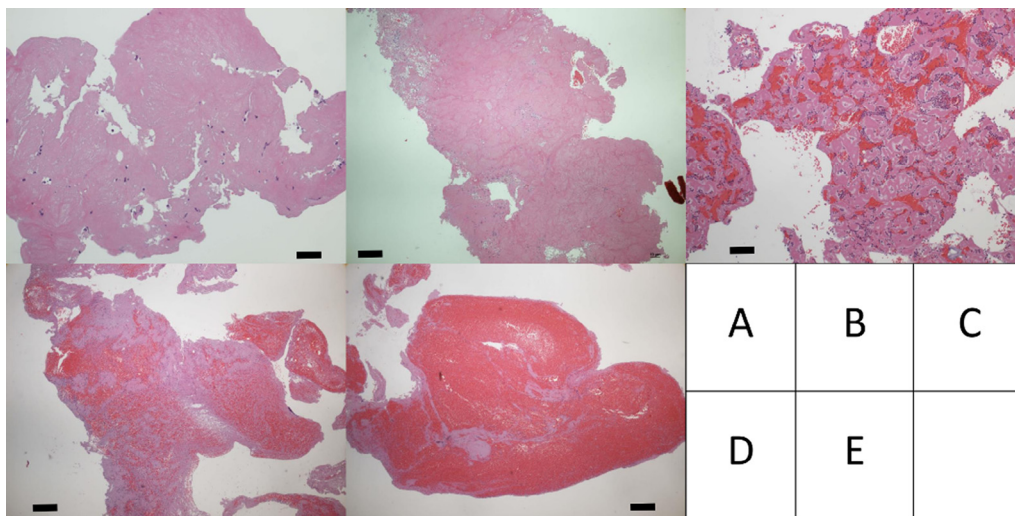


**Figure 2.** Bar graph demonstrating the proportion of the area of each hematological component in the thrombus. Abbreviations: ATBI, atherothrombotic brain infarction; CE, cardiogenic embolism; ESUS, embolic stroke of undetermined source; RBC, red blood cells; WBC, white blood cells.

tained extremely higher proportion (>90%) of fibrin than thrombi from other causes. In addition, high levels of plasma D-dimer and fibrin degradation product of patients with Trousseau syndrome suggested hypercoagulation, although they did not reach international DIC criteria.<sup>3</sup> Taken together, our result supports that Trousseau syndrome-related thrombi that occluded cerebral large vessels were caused by emboli from NBTE associated with cancer-related hypercoagulation. The detection rate of vegetation in NBTE was 18% by transesophageal echocardiography,<sup>8</sup> and the rate was lower

by transthoracic echocardiography.<sup>9</sup> Thus, it is no wonder that vegetation was not detected by transthoracic echocardiography in either of our Trousseau cases.

Histological findings obtained in this study give an insight into potential treatment of Trousseau syndrome. Although first-line treatment for preventing recurrence of embolism in Trousseau syndrome is anticoagulation therapy,<sup>10</sup> the optimal anticoagulant drug remains undetermined. Because thrombin mediates conversion of fibrinogen into fibrin, selective thrombin inhibitor including dabigatran, or direct Xa inhibitor rivaroxaban and



**Figure 3.** Hematoxylin-eosin staining of the retrieved thrombi. In this staining, fibrin component is stained pink by eosin. Erythrocytes are depicted as red, and nuclei in the leukocytes are stained purple by hematoxylin. (A) CASE 1, (B) CASE 2, (C) ATBI 1, (D) CE 1, (E) ESUS in Figure 2. In Trousseau CASE 1 (A) and CASE 2 (B), almost all the parts of thrombi consist of fibrin. In ATBI 1 (C), the rates of fibrin, red blood cells, and white blood cells are comparable in the thrombus. In CE 1 (D), fibrin and red blood cells are almost equally included in the thrombus. In ESUS (E), the most part of the thrombus is red blood cells, with a small amount of fibrin. Scale bar = 200  $\mu$ m.

apixaban, may be more promising than warfarin. A previous study failed to demonstrate significant superiority of dabigatran over warfarin in preventing recurrent venous thrombosis associated with malignant tumors.<sup>11</sup> However, histological findings of venous thrombi in patients with tumor are not necessarily identical to those of arterial thrombi in Trousseau syndrome. Investigating efficacy and safety of selective thrombin inhibitor to prevent recurrence of Trousseau syndrome may be valuable. In addition, several randomized trials using rivaroxaban (official title "Efficacy and Safety of Rivaroxaban Prophylaxis Compared with Placebo in Ambulatory Cancer Patients Initiating Systemic Cancer Therapy and at High Risk for Venous Thromboembolism"; URL <https://clinicaltrials.gov/ct2/show/NCT02555878>) or apixaban<sup>12</sup> are ongoing. The present study is the first report describing histological findings of thrombi retrieved from large cerebral vessels associated with Trousseau syndrome. We hope histological findings described here may facilitate further research of clinical entity and treatment of Trousseau syndrome.

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