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Case Report

Triple Thrombectomy for Trousseau Syndrome: Case Report and Review of the Literature of Stroke Intervention in Cancer-associated Thrombus

Catherine Wassef,[1] Audrey Grenga,[1] Bruce Goldman,[2] and Thomas Mattingly[1]

Objective: There are few papers regarding repeat mechanical thrombectomy or thrombectomy for Trousseau's related stroke. We present a unique case of repeat thrombectomy due to Trousseau's syndrome affecting the same vessel in a patient with metastatic cancer.

Case Presentation: A 47-year-old male presented with a full left middle cerebral artery syndrome and a National Institute of Health Stroke Scale of 17, despite regular apixaban use. He underwent mechanical thrombectomy successfully but developed recurrent symptoms on postoperative day (POD) 6 while on warfarin. He underwent two additional thrombectomies, the final one requiring glycoprotein IIa/IIIb inhibitor for emergent implantation of intracranial stent. Successful recanalization (thrombolysis in cerebral infarction 2b) was achieved, and the patient was discharged home on dual antiplatelet therapy and enoxaparin on POD 10 after last thrombectomy, ambulatory and independent in his activities of daily living. The patient expired as a result of his metastatic disease 109 days after the third procedure and was ambulatory for 91 of those days.

Conclusion: This case illustrates the palliative aspects of mechanical thrombectomy and the complexities of anticoagulation management in patients with the metastatic disease Trousseau's syndrome.

Keywords ▶ cancer, stroke, Trousseau, repeat thrombectomy, anticoagulation

Introduction

Stroke or cerebrovascular accident (CVA) in cancer patients is a growing field of research. As patients are living longer with cancer, complications coexisting with the disease are increasing. There is controversy regarding the relationship of cancer with the risk of stroke. A retrospective study suggested that stroke patients have no higher risk of recurrent stroke than the general population (about 6%).[1)] However, a more recent literature indicates an increased risk of stroke, especially recurrent stroke, in cancer patients over the general population.[2)] There are multiple etiologies for stroke in cancer patients, including shared comorbidities (age and smoking), direct tumor embolus, radiation-induced large vessel disease, inflammation, and paradoxical emboli secondary to venous thrombi. There are a few case reports of mechanical thrombectomy for cancer-related stroke, and of these, only one involved repeat thrombectomy >24 hours from initial embolectomy and none involved three embolectomies in the same vessel.[3–6)] We present an unusual case of repeated thrombosis, and subsequent thrombectomy, of the same intracranial territory. Our aggressive approach of triple thrombectomy for this patient resulted in preservation of his ability to communicate and ambulate until he ultimately passed due to his underlying cancer. We believe that mechanical thrombectomy, although aggressive, is an appropriate palliative procedure in select patients with end-stage metastatic disease. Nuances of anticoagulation management unique to this oncology cohort are illustrated by this case.

[1]*Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA*
[2]*Department of Pathology, University of Rochester Medical Center, Rochester, NY, USA*

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Corresponding author: Catherine Wassef. Department of Neurosurgery, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14618, USA
Email: catherine_wassef@urmc.rochester.edu

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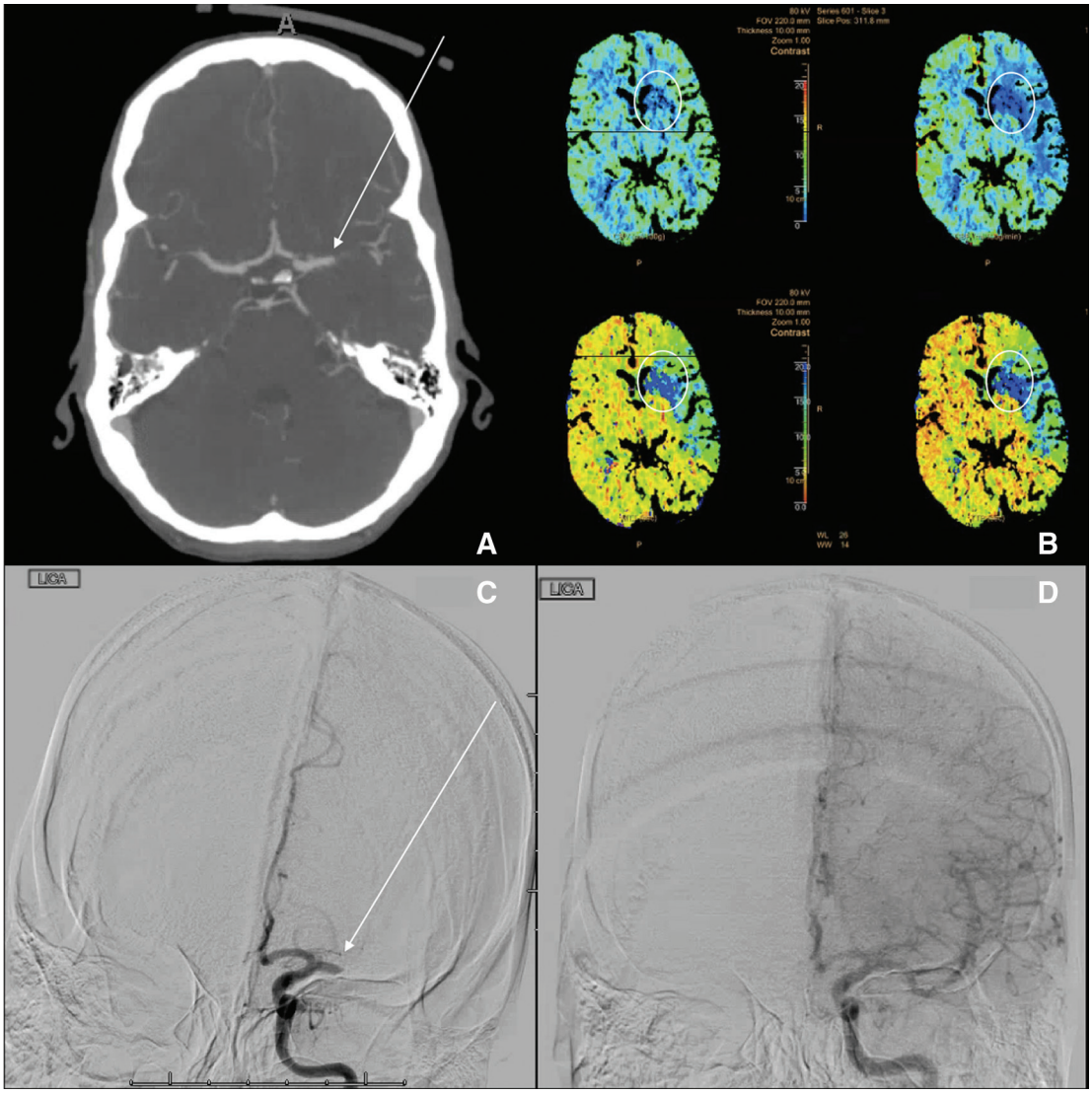

Fig. 1 (**A**) Axial CTA revealing left M1 occlusion (white arrow). (**B**) Postprocessing CT perfusion revealing mismatch between CBV (top left) and time to perfusion (bottom right), indicating a significant penumbra. Note core infarct in caudate and basal ganglia, which appears to have low blood volume and high time to perfusion (white circles). (**C**) Anteroposterior view DSA revealing left M1 occlusion (white arrow). (**D**) DSA revealing TICI 3 recanalization of left MCA territory. CBV: cerebral blood volume; MCA: middle cerebral artery; TICI: thrombolysis in cerebral infarction

Case Report

A 47-year-old male diagnosed with pancreatic cancer 1 month prior to status-post palliative biliary stent placement and right lower extremity deep vein thrombosis (DVT) was on apixaban use and chemotherapy. He presented to the hospital within 20 minutes of a witnessed onset left middle cerebral artery (MCA) syndrome (National Institutes of Health Stroke Scale [NIHSS] 17). Relevant laboratory studies included international normalized ratio (INR) of 1.5, prothrombin time (PT) of 17.5, and platelet count of 57000. He did not receive tissue plasminogen activator (tPA) due to active apixaban use. CTA demonstrated a left M1 occlusion with sizeable penumbra (**Fig. 1**), so the patient was taken for emergent thrombectomy by the endovascular neurosurgery team. The procedure was completed in three passes—two passes with direct aspiration and a third pass with intra-arterial tPA and Trevo stent retriever —and resulted in thrombolysis in cerebral infarction (TICI) 3 recanalization (**Fig. 1**). Postoperatively, the only residual deficit was a left inferior temporal visual field defect.

Post-procedure MRI revealed a small amount of subarachnoid hemorrhage in the left Sylvian fissure and infarct in the left basal ganglia and insula (**Fig. 2**). Routine stroke workup

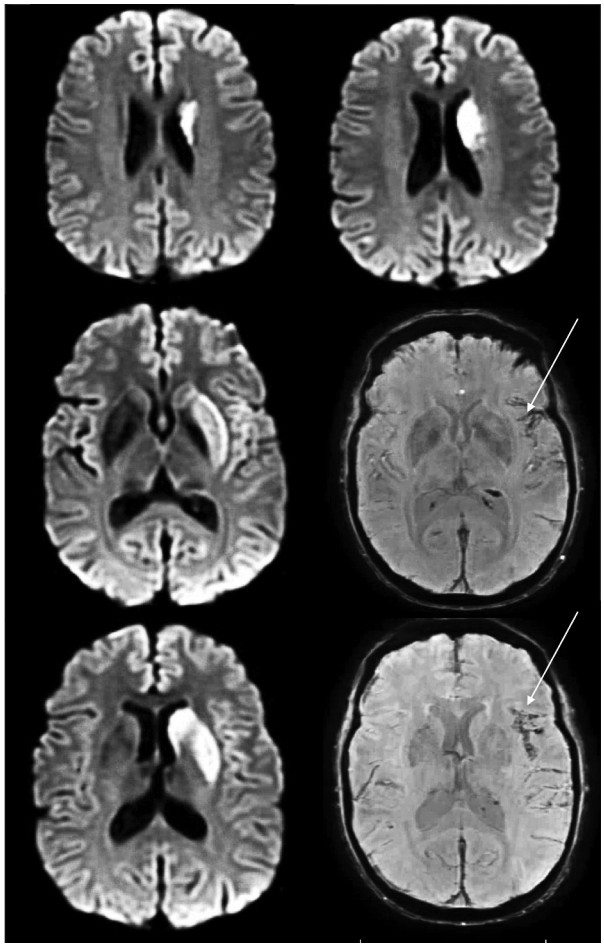

Fig. 2 DWI and SWI images showing left caudate and basal ganglia infarcts with minimal subarachnoid hemorrhage (white arrows) in Sylvian fissure post embolectomy. DWI: diffusion-weighted imaging; SWI: susceptibility weighted imaging

including transthoracic echocardiogram was performed, and there was no patent foramen ovale or shunting. Transesophageal echocardiogram was not warranted due to the sufficient quality of the transthoracic echo. Of note, D-dimer levels and thromboelastogram were not obtained. Since the patient suffered from a CVA while taking apixaban for a preexisting DVT, enoxaparin was recommended, but the patient's cachexia made injection therapy difficult. Therefore, the patient was placed on intravenous (IV) heparin bridge to warfarin. INR reached 4.1 on postoperative day (POD) 6, and heparin drip was discontinued on the same day. At this time, PTT was 139.4, with a platelet count of 383000.

Approximately, 3 hours after heparin drip was discontinued, the patient developed recurrent aphasia and right-sided hemiparesis, with an NIHSS of 17. CTA revealed partial left internal carotid artery (ICA) terminus occlusion (**Fig. 3**). The patient was brought to the endovascular suite within 1 hour of onset, and TICI 2b was achieved with two passes utilizing clot suction and intra-arterial tPA (**Fig. 3**). Postoperative examinations demonstrated resolution of his symptoms. Approximately 4 hours later, the patient again developed aphasia and right hemiparesis. Imaging revealed a large salvageable penumbra within the left MCA territory. Angiography confirmed a new ICA terminus occlusion. Decision was made to repeat thrombectomy.

Given the recurrent pattern of thrombosis within the same territory (**Fig. 3**), a local endothelial process, perhaps dissection, was suspected. Following two passes to reopen the MCA, an intracranial stent was placed to improve the probability of patency. The patient was loaded with tirofiban, and a low-profile visualized intracranial stent (LVIS Blue; MicroVention, Aliso Viejo, CA, USA) 4 mm × 23 mm was placed from the supraclinoid ICA into the left M1 (**Fig. 3**). TICI 2b recanalization was achieved.[7]

Following the third thrombectomy, the patient had residual expressive aphasia but retained the ability to answer "yes/no questions" and to ambulate. He was discharged to home on POD 10, on aspirin and clopidogrel to prevent stent thrombosis, and full-dose enoxaparin for systemic anticoagulation. He passed away 3.5 months after his last embolectomy, but was ambulatory until POD 90.

Discussion

Trousseau syndrome was defined in 1865 by Armand Trousseau to describe the tendency of oncologic patients to experience multiple thrombotic events secondary to a malignancy-associated hypercoagulation disorder.[3] There are now multiple reports of mechanical thrombectomy for Trousseau's syndrome; however, recurrent thrombectomy for stroke is uncommon.[3–5,7–10] In two large series, recurrent thrombosis was reported at about 2%, although not all of these received repeat intervention.[6,11] These series differ on their impression of the impact of recurrent thrombosis. In one series, recurrent thrombosis appeared to have a significant negative effect.[6] In another case series of repeat thrombectomy, the authors achieved mRS 0–2 in more than half of patients. One of them included a 32-year old who underwent thrombectomy three times (in two different vascular territories). We agree that thrombectomy for acute ischemic stroke is consistent with maintenance of quality of life, even if that means addressing a recurrently occluding vessel.[3] Our case is unique in that we performed three successful thrombectomies in the same vascular territory in an anticoagulated patient with end-stage metastatic

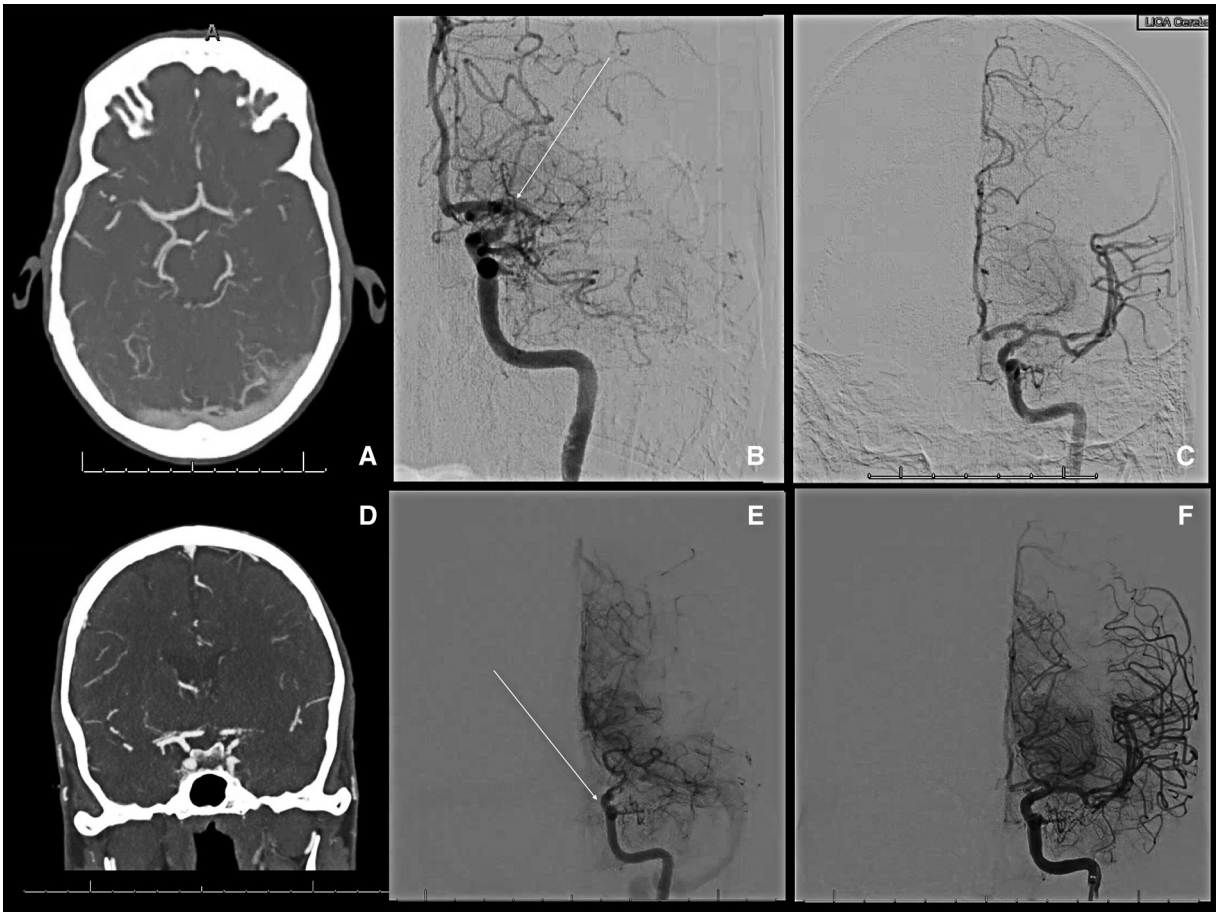

Fig. 3 Top row represents second embolectomy. (**A**) Axial CT angiogram reveals left ICA terminus occlusion (white arrow). (**B**) AP view of left internal carotid injection reveals occlusion at the left M1 origin. (**C**) AP view of left ICA demonstrates recanalization of MCA with irregular lumen of the M1 and M2 branches. Bottom row represents third embolectomy. (**D**) CTA reveals clear left ICA terminus occlusion (white arrow). (**E**) AP view of left ICA terminus occlusion with preserved PCOM and ophthalmic origins preembolectomy and postembolectomy. (**F**) Note improved filling of MCA branches relative to second embolectomy status post stent. AP: anteroposterior; ICA: internal carotid artery; MCA: middle cerebral artery; PCOM: posterior communicating artery

disease, ultimately restoring communication and motor function for the remainder of his life.

Common themes that emerge from these reports include frequent exclusion from IV tPA, presence of fibrin-rich clots, and a higher incidence of recurrent occlusion. Our case shares all of these features. Our patient presented with the combination of preexisting DVT and newly formed CVA while on anticoagulation. The patient was excluded from IV tPA due to current apixaban use. The clot pathology from the first thrombectomy was indeed a fibrin- and platelet-rich white clot with minimal red blood cells, which is consistent with a Trousseau's thrombus (**Fig. 4**).

There is debate about the relationship between cancer and stroke. Although older theories point to common risk factors for both stroke and cancer (i.e., smoking, age), newer hypotheses suggest that cancer causes a prothrombotic state.[1,12] Recent literature suggests that stroke risk is indeed

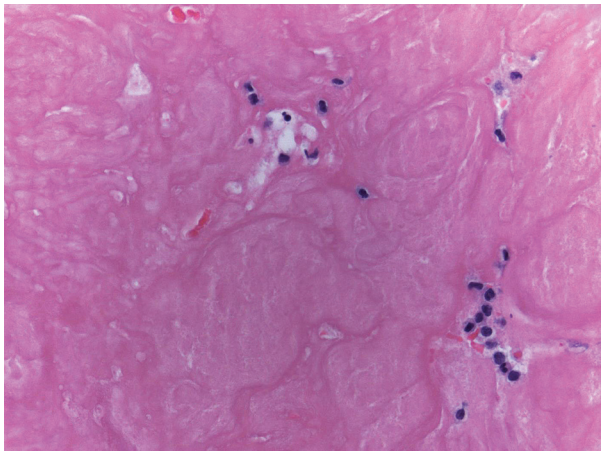

Fig. 4 Hematoxylin–eosin staining of thrombus obtained from the first embolectomy. This thrombus is rich in fibrin, which is stained pink by eosin. Note the acellular appearance and absence of red blood cells, which are abundant in standard acute blood clots.

higher for cancer patients, occurring even before the oncologic diagnosis and continuing for some time after the treatment has begun.[8] The mechanism for this increase is not entirely elucidated, but D-dimer has emerged as a marker.[13]

D-dimer levels are associated with decreased survival in a series of cancer-associated strokes.[14,15] D-Dimer levels can decrease with anticoagulation, regardless of the type of anticoagulation applied.[14–16] Unfortunately, a D-dimer level and full hypercoagulation panel were not ordered on our patient because the etiology was presumed to be cancer-related hypercoagulability. A hypercoagulability panel and D-dimer may have been useful in determining the optimal anticoagulation plan and possibly have prevented the second stroke and the third stroke.

An optimal anticoagulation regimen for cancer-associated stroke is unclear. While guidelines for venous thromboembolism prophylaxis and treatment in cancer suggest that low-molecular-weight heparin (LMWH) is superior to unfractionated heparin (UFH) or warfarin, no such guidelines exist for cancer-associated stroke.[17] Interest in novel oral anticoagulants (NOACs) or direct thrombin oral anticoagulants, which do not require monitoring, has been tempered by a suggestion of increased hemorrhagic complications, especially with gastrointestinal and genitourinary cancers. Several observational studies examining anticoagulation regimens in cancer-related stroke report cases in which an individual had a stroke on one agent and was changed to a different agent. These anticoagulation regimens utilized UFH, LMWH, warfarin, and aspirin.[8,14–16,18] Our patient arrived having an event on an NOAC, developed recurrence on therapeutic warfarin, and ultimately was placed on LMWH along with dual antiplatelet agents for the intracranial stent.

Given the multiple agents used for secondary prevention and the many putative causes of CVA in cancer patients, it may be appropriate to monitor D-dimer levels for response while determining an optimal anticoagulation regimen. If there is a suspicion of cancer-associated stroke, it is reasonable to start with therapeutic enoxaparin for secondary prevention while the secondary stroke workup proceeds. This decision needs to be weighed against hemorrhagic transformation in the stroke territory and the presence of more typical atherosclerotic features, which often coexist in this population.

The effectiveness of acute intervention for cancer-associated stroke is debated in the literature. While there are case reports suggesting benefit to intervention, this population has decreased rates of IV tPA administration.[8] This may be due to pre-ictus anticoagulation regimens such as in our case.[9] A single-center retrospective study of acute stroke treatment found 49 patients with acute stroke and coincident cancer, but only 12 underwent acute stroke treatment.[10] Although a 90-day mortality was just less than 50%, they noted a drop in median NIHSS from admission to discharge, and just over half of the patients were discharged to home or rehabilitation. It is likely that the natural history of neoplastic disease is the determinant of a 90-day outcome, so mortality rates and mRS are not an appropriate measure of effectiveness in this cohort.

In light of this, we argue that stage IV cancer with a likely terminal prognosis should not preclude a patient from consideration of endovascular intervention for acute stroke. Our patient was ambulatory and independent prior to presentation (mRS 0) and was discharged home on POD 10 after the last procedure, still ambulatory. Based on his degree of presenting deficit, he would have been discharged to a nursing facility, had it not been for repeated recanalization of his left hemisphere. Owing to our intervention, he was able to spend his final months at home.

Conclusion

Patients are chosen for embolectomy based on a host of factors, one of which is comorbidities. We argue that cancer prognosis should not be a large determinant factor in deciding on intervention, because quality of life can be significantly improved with a successful intervention. Our patient presented with a full left MCA syndrome and walked out of the hospital 16 days later, with comprehension intact and some retained expressive capacity. His stage IV pancreatic cancer diagnosis was not a deterrent in pursuing repeat embolectomy but rather a motivating factor in that decision. We believe that quality of life in the final stages of cancer can be preserved if the imaging is favorable. This case also points to the complexities in managing the hypercoagulable state that underlies these events.

Disclosure Statement

The authors have no financial relationships to disclose.

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