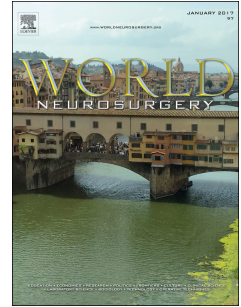


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Plateletpheresis: non-operative management of symptomatic carotid thrombosis in a patient with reactive thrombocytosis.

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Introduction:

Extracranial carotid artery intraluminal thrombus is an important cause of acute ischemic stroke or transient ischemic attack (TIA). It is a rare condition and the actual incidence remains unknown. The most common pathology associated with an intraluminal carotid thrombus is underlying atherosclerosis.¹ In cases where an underlying plaque is not identified, the condition may be associated with a hypercoagulable state, use of CNS stimulant drugs, iron deficiency anemia, or thrombocytosis.² Few case reports describe the association between reactive thrombocytosis (RT) and stroke. Thrombocytosis can occur as a response to a variety of stimuli such as iron deficiency, infections, trauma, malignancies, inflammation, hemorrhage and burns. Currently there are no clear recommendations for treatment of ischemic stroke associated with thrombocytosis. Plateletpheresis has been suggested as an accepted temporizing measure to reduce platelet count in patients with thrombocytosis associated active thrombosis; however, there is no reported case of its use in acute ischemic stroke.³

Case Report:

A 55-year-old female with past medical history of menorrhagia due to uterine fibroids who presented to the Emergency Department (ED) with acute onset left-sided weakness and left facial droop 4.5 hours prior to the arrival. By the time of her evaluation in ED the neurologic deficits had almost completely resolved except for left hemisensory deficit, making her National Institute of Health Stroke Scale (NIHSS) 1. The initial non-contrast computed tomography scan (CT) was non-revealing. Laboratory results revealed mild hypochromic anemia and a platelet count of $1014 \times 10^3/\text{mL}$. She was not a candidate for thrombolytic therapy due to the time window and her mild non-disabling residual deficit. Thirteen hours after admission she had acute worsening of the neurological symptoms. Her NIHSS was now 18 (LOC 1 gaze, 2 visual fields 2 facial palsy 2 left arm 3 left leg 3 sensory 2 dysarthria, 1 extinction 2). A CT angiogram showed an acute ischemic infarction involving the right middle cerebral artery territory with non-occlusive intraluminal filling defect within the right carotid bulb (Figure 1a and 1b). The patient was immediately transferred to the Neuro Intensive Care Unit and initiated on antiplatelet therapy with aspirin 325 mg and a heparin intravenous infusion. An MRI Brain without contrast showed acute infarction involving the right middle cerebral artery (MCA) territory (Figure 2).

Peripheral blood smear showed microcytic hypochromic red blood cells, occasionally pencil shaped and increase in platelet number with variation in size. Janus kinase 2 (JAK2) mutation was negative. She was also ruled out for other hypercoagulable states. Anemia work-up confirmed severe iron deficiency anemia (iron level 11, percent saturation 2.5% and ferritin 3) and mild Vitamin B12 deficiency (305 pg/mL). After ruling out a myeloproliferative neoplasm, the cause of her elevated platelet count was determined to be due to reactive thrombocytosis secondary to iron deficiency anemia.

A carotid Duplex revealed a mobile thrombus poorly adhered to the arterial wall at the bifurcation of the right extracranial carotid artery (Figure 3). A Transcranial Doppler (TCD) demonstrated a total of 26 high intensity transient signals (HITS) suggestive of artery-to-artery microemboli during 15 minutes of continuous R MCA insonation. She was not a candidate for immediate surgical thrombectomy due to high risk of re-thrombosis in the setting of persistent severely elevated platelet count. One cycle of plateletpheresis was performed on day 3, which dropped her platelet count to $400 \times 10^3/\text{mL}$ that remained stable during her entire admission.

On day 4 a repeated carotid duplex showed no further evidence of carotid thrombus or underlying carotid plaque. Repeat CT angiogram on day 4 showed persistent thrombus but noted a significant decrease in its size as compared to the prior study. Complete resolution of the carotid thrombus was confirmed on following CT angiogram on day 10 of the admission (Figure 4). She was discharged from the hospital on day 12 with enoxaparin for 4 weeks and aspirin 325 mg indefinitely. She was continued on ferrous sulfate and cyanocobalamin supplementation.

Discussion:

Optimal management of extracranial carotid artery acute intraluminal thrombus remains a topic of debate despite the high risk of new or recurrent ischemic events due to either distal migration of emboli or progression to complete carotid occlusion. Medical management with anti-platelet therapy, anticoagulation or early versus delayed revascularization are acceptable treatment approaches. The therapeutic approach is guided mostly by anecdotal experience rather than strong prospective clinical evidence.

Elevated platelet count can be due to either a myeloproliferative process or a reactive response to an inciting condition such as iron deficiency, infection, inflammation, hemorrhage, burns, trauma or malignancies.³ It is well established that a low platelet count has good correlation with increased risk of hemorrhage; on the contrary the correlation between high platelet count and the risk of thrombosis is unclear. The magnitude of thrombocytosis does not correlate well with risk of thrombosis.⁴ Some data suggests that platelet count greater than $1500 \times 10^3/\text{mL}$ has a greater risk of hemorrhage rather than thrombosis due to acquired von Willebrand factor deficiency.³ Therefore, it is the abnormal platelet aggregation and platelet function rather than the absolute platelet count which determine the risk of thrombosis.⁵

Few other case reports have described thrombocytosis related to iron deficiency anemia resulting in an internal carotid artery thrombus with acute stroke.^{4,5,6,7,8,9} Our case is the first to describe the use of plateletpheresis in the acute management of thrombocytosis-induced acute carotid artery thrombosis leading to ischemic stroke. There are no clear recommendations for the treatment of acute ischemic stroke associated with severe thrombocytosis and thromboembolic complication. It has been established that patients with essential thrombocytosis (ET) together with age > 60 years, prior thrombo-hemorrhagic events, and a platelet count of $> 1500 \times 10^9/\text{L}$ should be treated urgently.³ In contrast, asymptomatic patients with secondary thrombocytosis may not require platelet

reduction given their lower risk of thrombotic or hemorrhagic sequelae. Platelet reduction can be accomplished with hydroxyurea and platelet-selective anagrelide, as well as with plateletpheresis. The choice and intensity of platelet reduction depends on the severity of thrombocytosis as well as the individual risk of thrombotic or hemorrhagic event.³

The use of plateletpheresis has been described in the setting of thrombocytosis related to chronic myeloproliferative leukemia. According to the American Society for Apheresis (ASFA), plateletpheresis is currently second line therapy for symptomatic primary thrombocytosis while its role is not well established in the setting of prophylactic high-risk ET or secondary thrombocytosis.^{3,10} Elective plateletpheresis should also be considered in patients at increased risk of major hemorrhage when hydroxyurea is contraindicated or in situations when the onset of action of hydroxyurea is too slow, such as the requirement for emergent surgery. Plateletpheresis has effects on coagulation parameters by decreasing pro-thrombotic effect of factor VIII, fibrinogen, anti-thrombin, protein C, and protein S levels. Its efficacy is partly related to the selective removal of the larger, dysfunctional platelet population.³ Each procedure lowers the platelet count by 30–60%. The final platelet goal should be determined on case-by-case basis, but a platelet count of $\leq 600 \times 10^9/L$ may be sufficient.¹¹ Although anecdotal case reports have described a potential benefit of plateletpheresis with secondary thrombocytosis¹¹, rationale is undefined and efficacy unproven. Our patient underwent plateletpheresis on the third day of admission with successful platelet count reduction after one cycle.

Our patient was also started on anticoagulation therapy with heparin infusion and aggressive iron supplementation. Aggressive medical therapy and follow-up neuroimaging constitutes a reasonable approach to avoid the need for urgent carotid endarterectomy with the presumption that in the setting of moderate to large acute ischemic stroke there is a relatively higher risk of distal arterial thromboembolism and hemorrhagic transformation after the carotid revascularization. Moreover, in cases with extreme thrombocytosis immediate surgical thrombectomy may be contraindicated due to high risk of recurrent thrombosis in the setting of persistently elevated platelet count. Thus, urgent cytoreduction, and correction of the anemia with transfusions as needed and iron replacement should be undertaken.

Our patient showed complete resolution of the carotid thrombus prior to discharge, without evidence of underlying plaques in the carotid arteries to require any surgical intervention, proving that plateletpheresis is safe and efficient in the acute setting of an ischemic stroke due severe thrombocytosis-induced acute carotid artery thrombosis.

Conclusion:

Severe iron-deficiency anemia with or without reactive thrombocytosis is an important risk factor for development of ischemic stroke, particularly in young adults. Treatment should be focused on correcting the inciting factor, i.e., anemia, sepsis, trauma, or burn, and the reactive thrombocytosis. Medical management with short-term anticoagulation therapy and follow-up vascular imaging is a reasonable approach for these patients to minimize risk of embolization, reduce the risk of recurrent thrombosis and potentially avoid the need for surgical carotid revascularization.

To our knowledge this is the first reported clinical case where plateletpheresis was used in the acute setting as part of the medical management of an acute carotid artery thrombosis secondary to severe thrombocytosis. Plateletpheresis was safe and efficient in reducing the platelet count after only one cycle and most likely contributed to the rapid disappearance of the acute carotid artery thrombosis.

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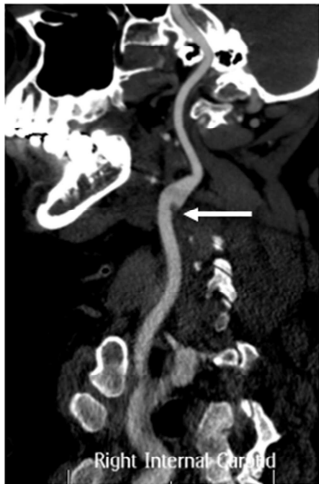
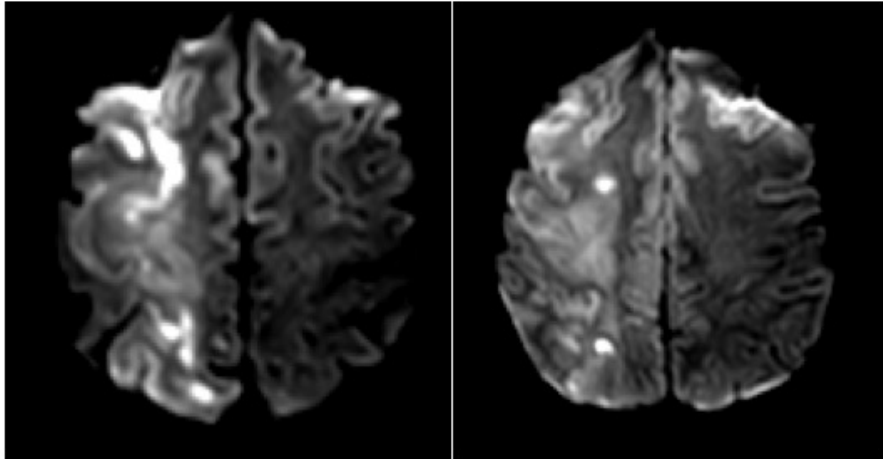


Figure 1a and 1b. Initial CTA showing filling defect within the right carotid artery. (arrow)

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Figure 2



MRI showing Acute right MCA ischemic infarction involving right frontal, parietal and temporal lobes as well as right caudate head, basal ganglia and insular cortex (not shown)

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Figure 3. Poorly adhered intraluminal carotid thrombus (arrow).

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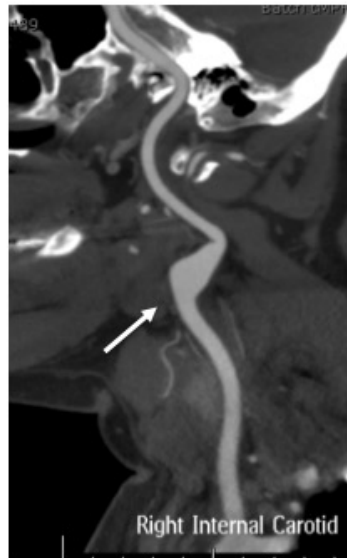


Figure 4. Follow-up CTA, day 10 showing resolution of filling defect. (arrow).

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Highlights

- Acute carotid thrombus is rarely caused by reactive thrombocytosis.
- Surgical revascularization in the acute phase may be high risk due to risk of embolization.
- Platepheresis is safe and efficient in the acute management with the aim to stabilize platelet count and dissolve the clot burden.
- Serial vascular imaging is necessary during this process to ensure decrease in clot size and aid in the risk-benefit decision making if a surgical approach is ultimately necessary.

Abbreviations

TIA – Transient Ischemic Attack

RT – Reactive Thrombocytosis

ED – Emergency Department

NIHSS – National Institute of Health Stroke Scale

CT – Computed Tomography

CTA – Computed Tomography Angiography

LOC – Level of Consciousness

TCD – Transcranial Doppler

HITS – High Intensity Transient Signals

ASA – acetylsalicylic acid, or aspirin

ET – essential thrombocytosis