Acute Carotid Stent Thrombosis in an Ultrarapid Clopidogrel Metabolizer: Case Report and Literature Review

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Abstract

Introduction: Carotid angioplasty and stenting (CAS) represents an effective procedure for treating carotid artery disease. The acute in-stent thrombosis is an extremely rare complication of CAS especially when it occurs postprocedurally during the first 24 hours. Improper antiplatelet therapy or poor response to antiplatelet medications is known to be associated with a higher risk for in-stent thrombosis during early postprocedural period following a successful intervention.

Material and Methods: A patient who experienced acute carotid in-stent thrombosis in early postprocedural period, is described. He had been taking dual antiplatelet therapy for 2 weeks before undergoing a successful CAS. Moreover, pharmacogenetics studies showed the patient to be a clopidogrel ultra-rapid metabolizer, which theoretically confers hyperresponsivity to medication. Alongside the report itself, a brief literature review of relevant sources pertinent to the case has been conducted.

Results: According to available literature, this is the first case report describing an ultra-rapid clopidogrel metabolizer who underwent an uneventful CAS, but experienced acute carotid in-stent thrombosis in early postprocedural period. A rescue procedure included an endovascular intervention consisting of thrombectomy and local alteplase application, followed by postprocedural administration of intravenous eptifibatide. At discharge, patient's dual antiplatelet therapy included ticagrelor instead of clopidogrel.

Conclusion: Acute carotid in-stent thrombosis is a highly unexpected complication of CAS, and can occur despite ultra-rapid clopidogrel metabolism-trait.

Keywords: Angioplasty, Carotid Thrombosis, Clopidogrel, Cytochrome P-450 CYP2C19, Stents

Introduction

Acute carotid stent thrombosis is an extremely rare event, with five case reports describing its occurrence in the first 24 hours postprocedurally [1–3]. Direct procedural causes of stent thrombosis include vessel injury, atheroma prolapse, and kinking or coiling of internal carotid artery (ICA), whereas improper antithrombotic regimen and a tendency to hypercoagulability appear as notable risk factors when considering early postprocedural complications [1,2,4]. By authors' knowledge and available literature (per Pubmed and Google Scholar database searches; current as of March 2019), this is the first case of a patient with ultra-rapid clopidogrel metabolism-trait exhibiting acute carotid stent thrombosis.

Case Report

A 55-year old male patient was admitted to neurology service for elective carotid artery stenting (CAS) procedure following a successful elective percutaneous coronary intervention (PCI) of the left anterior descending (LAD) coronary artery during the same hospitalization. Patient's medical history was notable for longstanding hypertension, hyperlipoproteinemia, type 2 diabetes mellitus, chronic bronchitis, post-traumatic stress disorder, and a NSTEMI myocardial infarction nine years ago, for which he underwent LAD stenting. Six months before reported hospitalization, a head and neck magnetic resonance angiography (MRA) and subsequent consults were done in a regional hospital. The MRA revealed a subocclusive stenosis of the left internal carotid artery (ICA). Upon a neurological exam for asymptomatic carotid stenosis at that time, surgical treatment was not recommended. Due to progressive anginal symptomatology the patient was ultimately admitted at our hospital for the aforementioned LAD stenting. Patient's postprocedural dual antiplatelet therapy (DAPT) included clopidogrel 75 mg daily and acetylsalicylic acid 100 mg daily. Head and neck multi-slice computed tomography angiography (MSCTA) confirmed previously shown subocclusive stenosis of the left ICA and CAS procedure was recommended (Figure 1A). The patient was on DAPT for 14 days prior to CAS. Platelet reactivity was checked with VerifyNow-P2Y12 point-of-care device which confirmed that a therapeutic range had been reached. The CAS procedure was performed in a routine manner during which 5000 IU of heparin were administered. Predilation was performed with 4.5 x 20 mm (Aviator Plus; Cordis) balloon, and a carotid stent (Xact 8–6/40; Abbott Vascular) was placed, achieving full extension (Figure 1B). Embolic protection device was not used. Postprocedural angiographic runs did not show residual stenosis nor signs of distal embolization or other intracranial complications.

The patient manifested global aphasia and right hemiparesis 2 hours after CAS procedure. Brain MRI scan was negative for acute ischemia or bleeding, whereas head and neck CTA demonstrated an acute stent thrombosis (Figure 1C). Intracranial left ICA territory was reconstituted through anterior communicating artery crossflow.

The patient was immediately transferred to the angiosuite and digital subtraction angiography confirmed thrombosis of stent and occlusion of the ICA (Figure 1D). Long sheath was placed in the left common carotid artery and aspiration catheter (Sofia 6F; MicroVention) was appropriately placed in order to attempt pump-assisted thrombus aspiration. After several attempts, only partial recanalization was achieved and we decided to administer 20 ml of alteplase via microcatheter at

thrombosis site, followed by repeated thrombectomy. Despite pump-assisted thrombus aspirations and catheter-directed thrombolysis using alteplase, control angiography runs revealed thrombus progression (Figure 1E). Intracranial circulation was intact per periodic angiography throughout the procedure, and the patient began to recover despite thrombus formation.

We decided to finish the procedure and to administer a bolus of eptifibatide combined with continuous intravenous eptifibatide perfusion during a 12h-period while the patient was stationed at the intensive care. A head CT scan on the following day showed no acute changes. Prior to being discharged home on the third postprocedural day, a carotid artery CTA showed the appropriate positioning of left ICA stent without signs of significant residual stenosis (Figure 1F), while the previously described findings on right carotid artery bifurcation were stationary. Due to acute adverse event despite adequate periprocedural management, a pharmacogenetics analysis for *CYP2C19* and *MDR1* (*ABCB1*) polymorphism was done. The findings revealed intermediary *MDR1* transport activity and ultrarapid *CYP2C19* metabolism (genotype *17/*17). However, considering the incident, clopidogrel was discontinued as part of patient's DAPT, and ticagrelor 180 mg daily was given instead. Three months later, a scheduled follow-up CDFI exam demonstrated full stent patency with otherwise unchanged neck vasculature status.

Literature review and conclusion

Acute carotid stent thrombosis remains a rare complication of CAS, occurring during or after less than 1% of procedures [2,5]. According to the available literature, this is the 34th described case of carotid stent thrombosis in early period (<30 days), including all respective reports of such events as an intraprocedural complication [1–3,5–8]. In the most comprehensive review up to date in which 26 cases of early carotid stent thrombosis are presented, an algorithm for management of acute carotid stent thrombosis has been proposed [2]. This algorithmic approach distinguishes whether the complication occurred intra- or postprocedurally. In the latter case, which also pertains to our experience, an imaging study is recommended in order to evaluate the level of thrombosis, initially by ultrasound, but ultimately by angiography. Once confirmed, thrombectomy, thromboaspiration, and systemic thrombolysis with or without use of GIIb/IIIa inhibitors remain as equally valid options. Surgical exploration also represents an equally valid rescue option in cases when thrombosis is limited to stent area, whereas it is the ultimate step in cases when thrombosis extends beyond the stent. As seen in our case, but other before [2], multiple modalities may be used concurrently depending on individual patient characteristics and skills of professionals involved in the care.

Identifying the cause should help guide acute management, but also aid in adjustment of chronic treatment plan for patients. By clinical reasoning, inadequate antiplatelet therapy, thrombotic diathesis, or clopidogrel therapy hyporesponse is presumed as a likely culprit when the CAS procedure itself was successfully completed [1,2,4,6]. Regarding DAPT, it has been shown that 'resistance' rates to aspirin or clopidogrel range from 5-44%, respectively [9,10]. Therefore, when available, reasonable diagnostics in case of stent thrombosis include a wider set of coagulation tests with additional studies such as platelet aggregometry or pharmacogenetics, primarily for *CYP2C19* gene due to its salience for clopidogrel metabolism. The *CYP2C19* genetic polymorphism is comprised of 35 star (*) allele variants [11]. Heterozygous carriers of *2 or *3

variants are deemed intermediate metabolizers, whereas homozygotes are exhibiting poor metabolism. On the contrary, *17 trait confers rapid, and even ultra-rapid metabolism in case of *17 homozygosity [11]. Up to 50% of patients may belong to the category of poor or intermediate metabolizers which is linked with clopidogrel hyporesponsivity, while up to 5% are ultra-rapid metabolizers, a trait that theoretically confers greater risk for clopidogrel-caused bleeding diathesis. In case of clopidogrel or aspirin 'resistance', increased maintenance doses may bring benefits, though an alternative strategy is to switch to a different combination of antiplatelet drugs [9,10]. Current recommendations for ultra-rapid *CYP2C19* metabolizers do not endorse any changes in standard DAPT dosing [11].

Considering an uneventful PCI procedure and its postprocedural period, together with ultra-rapid clopidogrel metabolism-trait and a normal course during CAS procedure, the acute carotid in-stent thrombosis described in our patient is a seemingly paradoxical adverse event, with exact etiology still remaining elusive.

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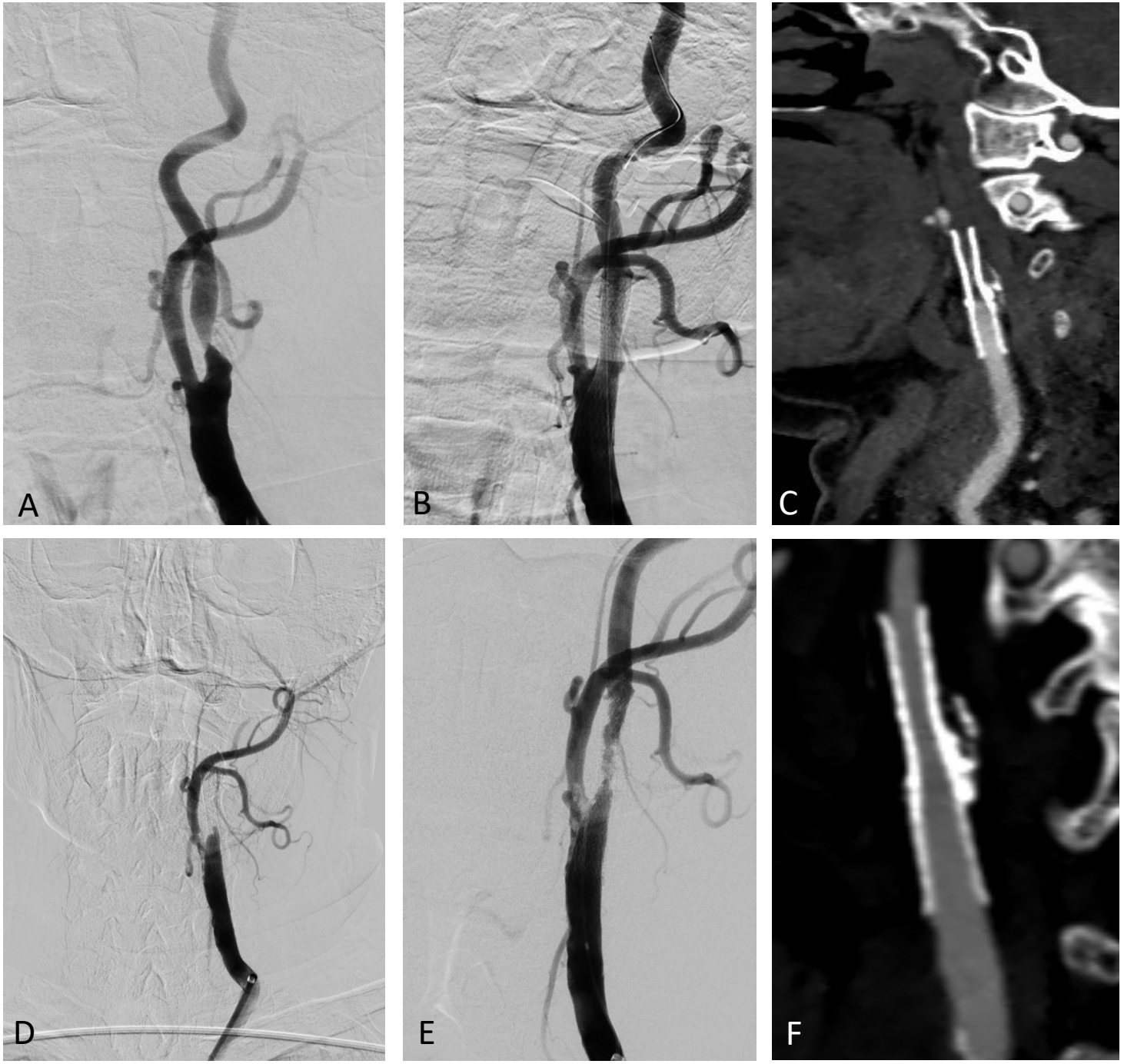
Figures

Figure 1. Figure 1. A, Severe asymptomatic stenosis of the left internal carotid artery. B, Carotid artery stenting (CAS) was performed. C, Computed tomography angiography (CTA) performed 2 hours after endovascular procedure showed acute carotid stent thrombosis. D, Digital subtraction angiography confirmed thrombosis and occlusion of the stent. E, Partial recanalization was achieved after repeated pump-assisted thrombus aspiration and intrathrombus Alteplase administration. F, Control CTA performed prior to discharge showed no signs of thrombosis and no significant residual stenosis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