

## Successful treatment of aortic arch mural thrombosis with low-dose, ultra-slow-flow thrombolysis: a case report and literature review

Rosina Albisinni,<sup>1</sup> Tommaso Marrazzo,<sup>2</sup> Arta Karruli,<sup>2</sup> Sabrina Manduca,<sup>3</sup> Giuseppe Nobile,<sup>4</sup> Nicola Galdieri,<sup>5</sup> Marisa De Feo<sup>6</sup>

<sup>1</sup>Unit of Infectious and Transplant Medicine, AORN Ospedali dei Colli-Monaldi Hospital, Naples, Italy; <sup>2</sup>Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy; <sup>3</sup>Unit of Ecocardiography and Endovascular Therapy, AORN Ospedali dei Colli-Monaldi Hospital, Naples, Italy; <sup>4</sup>Unit of Vascular Surgery, AORN Ospedali dei Colli-Monaldi Hospital, Naples, Italy; <sup>5</sup>Unit of Cardiac Anesthesia and Intensive Care, AORN Ospedali dei Colli-Monaldi Hospital, Naples, Italy; <sup>6</sup>Department of Cardio-Thoracic Sciences, University of Campania "Luigi Vanvitelli," Naples, Italy

### ABSTRACT

Aortic arch thrombosis represents a severe condition which usually requires surgical treatment in specialized centers. Treatments described in literature are mostly surgery or sodium heparin infusion. Here we describe an off-label use of alteplase in aortic arch thrombosis in a patient in whom sodium heparin treatment failed and surgery was not possible due to the site of thrombus. We report the case of a 34-year-old postpartum patient who was admitted to our hospital for aortic arch thrombosis. She had no genetic disorders for hypercoagulability, only a family history for ischemic cerebrovascular accident. As treatment with sodium heparin failed and surgery was not possible due to the site of thrombus, she received a low-dose, ultra-slow-flow treatment with alteplase for 75 hours with successful removal of the thrombus. No side effects from alteplase were observed. Considering the safety and efficacy in this patient, as well as the easiness by which it can be reproduced in the majority of clinical settings, this treatment may be a viable option in cases of aortic arch thrombosis when conventional treatments are not applicable or available.

Correspondence: Rosina Albisinni, Ospedale Monaldi, Piazzale Ettore Ruggieri, 80131 Napoli, Italy.  
Tel: +39.0817064154  
E-mail rosa.albisinni@ospedaledicolli.it

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### INTRODUCTION

Aortic arch thrombosis is a rare disease, with only a few cases described in literature mostly in patients with no major risk factors such as atherosclerosis, trauma, aneurism, hypercoagulable state,<sup>1,2</sup> few cases with essential thrombocytosis and malignancies,<sup>3-6</sup> and as consequence of atherosclerosis in different sites of aorta.<sup>7</sup> Pregnant women are at high risk for developing venous thromboembolic events and aortic dissection or rupture.<sup>8-10</sup> However, arterial thrombosis is not a common manifestation during pregnancy or postpartum period.<sup>9</sup>

As this disease is fatal, the first line of treatment is surgery as described in a previous case report,<sup>11</sup> also in 21 patients in a cohort of 38 patients with thrombus in ascending or aortic arch and in 88 patients in a meta-analysis study of 200 patients.<sup>1,2</sup> In patients with thrombus located in the aortic arch, surgery was the most common treatment.<sup>2</sup> Persistence after treatment was higher in anticoagulant group compared to surgery group (26.4% vs 5.7%).<sup>1</sup> As this disease is rare in postpartum patients with no major risk factors for arterial thrombosis, no data regarding treatment in such patients in particular when surgery, a first line treatment can't be performed or is not efficient, exists in literature. Here we describe a case of aortic arch thrombosis in a postpartum female treated with alteplase.

### CASE REPORT

A 34-year-old woman diagnosed with critical ischemia of left upper limb, was transferred to our hospital,

Monaldi Hospital from the Emergency Unit of another hospital in April 2021, where she was admitted for the onset of severe pain. She had a recent medical history of giving birth to a deceased fetus 2 weeks ago. The left arm appeared cold and cyanotic, radial pulse was not appreciable and the humeral one was hyposphymic. The motor capacity was preserved, however, burdened by intense painful symptoms. The patient who was alert and collaborating, was subjected to chest angiography and subsequently to selective angiography of the upper limb. The Computed Tomography angiogram showed a thrombus in the aortic arch between the origin of the left carotid artery and the left subclavian artery with a preserved flow and without signs of aortic dissection; echo-color-Doppler of the left upper limb evidenced occlusion of the humeral bifurcation with preserved mobility and sensitivity of the left hand. After consultation with a vascular surgeon specialist, the patient underwent endarterectomy with ineffective distal revascularization of the hand and digital compartment. A few hours after the first surgery, due to the pain, reduced mobility and sensitivity of the hand and the lack of the humeral pulse and the distal left radial and ulnar pulses, worsened by the absence of vascularization of the palmar and dorsal arch of the hand, we proceeded to new fogartization treatment followed by infusion of r-TPa (Alteplase) 2 mg per hour over the next 24 h. After 12 hours, despite the continuous infusion of thrombolytic, we detected the presence of tension in the muscle lodges of the forearm and hypothermic hand (retained mobility and sensitivity) and therefore acute compartment syndrome of the forearm and radiocarpal joint and fingers was diagnosed.

The appearance of the compartment syndrome is an indirect sign of partial effectiveness of a revascularization at least in the forearm area. However, due to the appearance of bleeding from the site of entry of the infusion catheter, thrombolysis was suspended, and coagulation was re-evaluated in consideration of the need to perform fasciotomy. The patient underwent a new fogartization with arterial revascularization of the humeral artery and ulnar artery with removal of thromboembolic material in both sites. Decompression of the volar area of the forearm was performed by extending the incision from the elbow to the wrist on the volar side of the forearm, also evacuating a small collection of blood and fluid from the muscle area.

48 hours after surgery, anticoagulation therapy with enoxaparin sodium 10000 UI every 12 h was started, and 72 hours after surgery acetylsalicylic acid at a dose of 300 mg per day was introduced.

After a few days, the surgical wound was treated with Vacuum Assisted Closure therapy (VAC therapy, -120 mmHg) to facilitate healing by secondary intention.

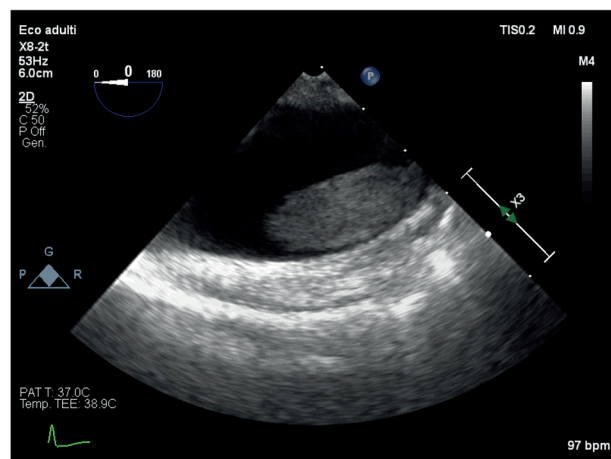
In anamnesis about two weeks before this episode, the patient gave birth by caesarean section to a deceased fetus

weighing 3,700 grams and underwent post-surgery anticoagulant therapy with low-molecular-weight heparin which lasted only for 10 days. The patient also reported a family history of arterial thrombosis (she reported ischemic ictal episode and persistent motor aphasia of the father at the age of 30). The patient had a Body mass index of 35, hypothyroidism in sub-optimal medical therapy; the study of coagulation factors associated with thrombosis such as natural anticoagulant showed normal C and S coagulation Proteins, Antitrombin III, absent heparin-induced platelet antibody, lupus anticoagulant, anticardiolipin antibodies and anti Beta-2 glycoprotein I. There was only a slight alteration of homocysteine, increased D-Dimer and significant mixed dyslipidemia (Table 1).

Genetic mutations associated with thrombophilia such as FV Leiden G1691A and FII G20210A were absent. Only MTHFR C667T in homozygosity was present.

Ninety-six hours after surgery, a parenteral anticoagulant therapy with warfarin initiated and she was re-assessed in terms of radiological exams with a CT angiography scan and a trans-esophageal echocardiography showing the thrombus in the aortic arch unchanged (dimension 1.3×3.2 cm) (Figure 1).

Ten days after vascular surgery and anticoagulant treatment start, due to the high risk for new embolic events, and in consideration of impossibility of carrying out cardiac surgery for the removal of the thrombus in the aortic arch, also in the absence of therapeutic alternatives and on the basis of the data in the literature describing the use of r-TPa (alteplase) thrombolytic treatment on thrombosis of cardiac prostheses also reported in pregnant subjects, thrombolysis treatment was initiated with a "low-dose, ultra-slow-infusion" protocol [25 mg in 25 hours repeatable up to 5 times starting when the values of international normalized ratio (INR) are  $\leq 1.7$ ]. The patient



**Figure 1.** Trans-esophageal echocardiography showing aortic arch mural thrombus before thrombolysis treatment.

gave consent to this treatment after she was explained the impossibility/failure of other treatments options.

She underwent a total of 75-hours therapy with a total dose of 75 mg of alteplase. No adverse event from this treatment was observed. Trans-esophageal echocardiography performed after treatment, showed no residue of the previously presented thrombotic formation.

At discharge, due to the patient's high body weight, she had indication for anticoagulant therapy with Vitamin K antagonists (VKA) (INR target 2.5-3) and acetylsalicylic acid at a dose of 300 mg per day. The literature regarding therapy with new Direct Oral Anticoagulants in obese patients suggest preferring treatment with VKA because of the lack of available safety and efficacy data. The wound on the left arm was periodically medicated and after a few days it healed. At 90 days follow up the patient continued treatment with VKA with INR range 2-3, and acetylsalicylic acid. No recurrent event is observed until now.

## DISCUSSION

This case presentation shows the efficacy and safety of low-dose, ultra-slow flow treatment in a postpartum patient following cesarian section. In literature limited data regarding treatment with parenteral anticoagulants in postpartum patients exists, with one case report describing a thrombophilic postpartum patient treated with sodium heparin.<sup>12</sup> Pregnancy is a high-risk condition for developing throm-

bosis as it satisfies the three elements of Virchow's triad specifically hypercoagulability, venous stasis and endothelial damage.<sup>13</sup> Major changes in coagulation parameters are fibrinogen increase, resistance to activated protein C and increase of fibrinolytic inhibitors levels.<sup>14</sup> However, these changes in pregnancy are associated more with venous thrombosis as arterial ones are very rare in pregnancy.<sup>9</sup> The patient apart from family history of cerebrovascular accident did not have other major risk factors for arterial thrombosis described in literature such as atherosclerosis, thrombocytosis, prothrombin alteration, deficit of anticoagulant protein C, S, deficit of antithrombin, presence of anticardiolipin antibodies or genetic disorders of coagulation factors such as FV G1691A, FII G20210A.<sup>15</sup>

The preferred treatment for arterial thrombosis is surgery compared to medical treatment. Surgery leads to lower rate of complications such as limb amputation and lower rate of recurrence.<sup>1</sup> However, in this case, thrombosis removal surgery was not possible due to the anatomical site of thrombus and possible side effects of anesthetics risk due to obesity. After an unsuccessful treatment with sodium heparin, we opted for an off-label treatment with alteplase with low-dose, ultra-slow-flow protocol, normally used in cardiac valve thrombosis,<sup>16,17</sup> which resulted successful. Low-dose ultra-slow flow infusion of tissue-type plasminogen activator was associated with low rate of nonfatal complications and mortality with a success rate of 90% in 114 patients with prosthetic

**Table 1.** Hematochemical and coagulation parameters.

Parameter	Hospital admission	Post thrombolysis
Red blood cells, cells/ $\mu$ L	3.290.000	3.220.000
Hemoglobin, g/dl	10.2	8.9
Platelet count, cells/ $\mu$ L	388.000	472.000
International normalized ratio	0.96	1.06
Activated partial thromboplastin time, sec	30	31
Fibrinogen, mg/d Ddimer, ng/ml	560/868	451/208
C reactive protein, mg/dl	9.16	1.2
Antitrombin III, %	130	105
Creatinine, mg/dl	1.07	0.7
Aspartate aminotransferase/Alanine aminotransferase, UI/L	14/18	14/27
Total bilirubin/Direct bilirubin, mg/dl	0.23/0.10	0.5/0.14
Creatine kinase, UI/L	46	21
Protein C, %	130	NA
Factor VIII, %	266	NA
Resistance to activated Protein C	2.24	NA
Protein S, %	71	NA
Lupus anticoagulant	1.24	NA
Antibodies anticardiolipin	Absent	NA
Anti B2 glycoprotein	Absent	NA
Homocystein, $\mu$ mol/L	20	NA

valve thrombosis with 120 different episodes between 2009 and 2013 in PROMETE TRIAL.<sup>18</sup>

Regarding pregnant patients with thrombosis, an 8-year timeline study on 24 patients with 25 pregnancies and 28 prosthetic valve thrombosis episodes treated with low dose ultra-slow flow t-PA showed that all episodes were treated successfully with only 2 episodes having bleeding as side effect.<sup>17</sup>

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## CONCLUSIONS

Considering the safety and the efficacy of this treatment in this patient, as well as the ease with which it can be reproduced in the majority of clinical settings, we suggest considering this treatment as an option in cases of aortic arch thrombosis when conventional treatments are not applicable or available.

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