In utero arterial thrombosis treated with recombinant tissue plasminogen activator in an infant of a diabetic mother: A case report and literature review

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A 36+5 days' gestation infant of a diabetic mother suffered arterial thrombosis with severe vascular occlusions in multiple limbs, especially of the left upper extremity. Although the mechanism remains elusive, the association between venous and arterial thrombi in infants and diabetic mothers has previously been established. Cases typically result in the amputation of the dysvascular limbs. In the present case, the use of selective angiography to administer recombinant tissue plasminogen activator allowed the left upper extremity to be salvaged with amputation of only the left thumb.

Key Words: Arterial thrombosis; Infant of diabetic mother; Thrombolytic treatment

Poor arterial vascularization of a limb presenting at birth is a rare but serious problem, with most reported cases occurring as a sequelae of umbilical artery catheterization, sepsis, congenital heart disease, thromboembolism or dehydration (1,2). It has previously been reported that infants of diabetic mothers (IDM) have an increased risk of both venous and arterial thrombosis (1,2). Traditional management is supportive, including hydration, nutritional support, cleaning of the wound, dressing changes and antibiotics to prevent secondary infections (3,4). Unfortunately, this conservative approach often leads to limb amputation at the level of the elbow, wrist or knee between 3 h and two months of age (5-8). We present a rare case of a female IDM who suffered arterial thrombosis that was aggressively treated with selective angiography to administer Alteplase (Genentech, USA), a recombinant tissue plasminogen activator.

CASE PRESENTATION

A female infant was born at 36+5 days' gestation to a 34-year-old G2A1 mother. The pregnancy was complicated by a mother with insulin-dependent diabetes mellitus who had been using insulin for two years. Although she required increased insulin during the pregnancy, her glucose levels were well controlled. At delivery, the infant weighed 2730 g (50th percentile), was 47 cm long (45th percentile) and had a head circumference of 32 cm (15th percentile). At 1 min and 5 min, Apgar scores were 9 and 10, respectively. Cyanosis and edema were present in both arms and the right leg, and the left upper extremity was particularly ischemic. Brachial and radial pulses were absent bilaterally and there was a delayed capillary refill of 3 s. Supportive therapy was immediately initiated, and the forearm was treated with topical flomazine and intravenous (IV) cloxacillin and acetaminophen for pain control. Complete blood count, disseminated intravascular coagulation screen and thrombophilia work-up were all within normal limits.

The patient was transferred to the authors' institution on day 3 of life. She was also found to be hypertensive, with a mean arterial

Une thrombose artérielle *in utero* traitée à l'aide d'une forme recombinante de l'activateur tissulaire du plasminogène chez le nourrisson d'une mère diabétique : rapport de cas et analyse bibliographique

Le nourrisson de 36+5 jours d'âge gestationnel d'une mère diabétique a subi une thrombose artérielle accompagnée de graves occlusions vasculaires dans plusieurs membres, notamment le bras gauche. Même si le mécanisme demeure flou, l'association entre les thromboses veineuses et artérielles chez les nourrissons et une mère diabétique est déjà établie. D'ordinaire, les cas entraînent l'amputation des membres dévascularisés. Dans le présent cas, le recours à l'angiographie sélective pour administrer une forme recombinante de l'activateur tissulaire du plasminogène a permis de sauver le bras gauche et d'amputer seulement le pouce gauche.

Figure 1) Angiography imaging of the patient's left arm pre- and post-Alteplase (Genentech, USA), a recombinant tissue plasminogen activator. **A** Pretreatment angiogram showing an intraluminal occlusive thrombus of the left axillary artery. **B** After administration of intra-arterial Alteplase 0.5 mg/kg/h proximal to the lesion, repeat angiography demonstrating patency of the patient's left axillary and brachial artery

pressure of between 67 mmHg and 78 mmHg, which necessitated the start of antihypertensive treatment with IV infusions of milrinone 0.5 mg/kg/min and nitroprusside 1.5 mg/kg/min.

Ultrasound showed multiple prominent collateral veins in the left forearm but was otherwise unremarkable. Magnetic resonance contrast angiography revealed bilateral subclavian, left brachial and left femoral arterial thrombosis (Figure 1). On the left side, the occlusive thrombus extended from the axillary artery to the brachial artery.

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Subsequently, the patient underwent immediate thrombolysis with intra-arterial Alteplase 0.5 mg/kg/h for 2 h. Repeat angiography post-thrombolytic therapy demonstrated patency of both upper limbs and the right leg. The patient was then given heparin 50 U/kg IV bolus followed by 25 U/kg/h IV infusion. From days 5 to 7, the patient was given Alteplase 0.5 mg/kg/h for 6 h daily after pretreatment with fresh frozen plasma to replenish plasminogen.

Throughout the hospitalization, the patient showed improvement, with perfusion to both arms and the right leg. However, scarring of most of the left upper extremity persisted and her left thumb remained necrotic. On day 37, the patient required debridement and a skin graft to her left forearm, as well as left thumb amputation. Her overall health continued to improve. On day 45, the antihypertensives were discontinued, and she was started on acetylsalicylic acid and discharged.

At six months of age, her arm had healed well and acetylsalicylic acid was discontinued. At three years of age, reconstructive surgery was suggested and the patient underwent left index pollicisation, which healed well with no postoperative complications.

DISCUSSION

Peripheral ischemia in an infant is rare. However, it is relatively more common in IDM. In a study of mothers giving birth at a hospital, IDM had a thrombosis rate of 15.8% compared with 0.8% in infants of nondiabetic mothers (1). Although the specific mechanism of increased thrombosis in IDM remains unclear, it is likely multifactorial with an interplay between genetic and environmental factors that lead to changes in the procoagulation, anticoagulation and thrombolytic pathways. Various authors have reported increased proaggregatory platelet endoperoxide levels, decreased anti-aggregatory vascular

prostacyclin levels (9), decreased plasminogen activity (6,7), protein C deficiency (10) and altered levels of fibrinolysis inhibitors, specifically increased fast antiplasmin and decreased slow antiplasmin levels (11). Compared with infants of nondiabetic mothers, thromboses in IDM were also reported to show more organization, calcification and earlier fatalities, with more than one-half of IDM expiring in utero, at birth or within the first 24 h of life (1,5).

An unusual case of arterial occlusion in an IDM is presented. Previously reported cases typically result in the amputation of the dysvascular limbs. Treatments used by other authors have included supportive therapy (5-8,12), hyperbaric chambers to supply adequate oxygen (3), thrombectomy (13) and fasciotomy (14). However, the treatment outcomes usually result in either amputation of the affected limb or death. In other cases, limbs were able to be salvaged with supportive treatment by allowing the ischemic areas to demarcate and slough off (4,15). However, these patients experienced long-term sequelae including shortening of bones and muscle contractures of the affected limb. In this case, aggressive therapy with Alteplase allowed for the affected limb to be salvaged with amputation of only the distal thumb.

Thrombolytic therapy in newborns has been used in a wide range of thrombotic conditions but indications for arterial thrombosis in IDM remain to be established. A combination of a thrombolytic, urokinase and anticoagulants have been used in three cases to prevent amputation in IDM (16-18). Thrombolytic use was successful within the first 24 h and when demarcation of the necrotic area has not yet been achieved. Thus, early use is critical. In the presented case, although treatment was delayed until the third day of life, the affected limb was successfully salvaged with the exception of the thumb using intra-arterial Alteplase and intravenous heparin in an IDM.

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