

ARTERIAL THROMBOSIS IN UTERO CAUSING ARM GANGRENE IN THE INFANT OF A DIABETIC MOTHER

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Summary. Gangrene of a limb presenting at birth is rare and has heterogenous etiology. Approximately 25% of the cases have been reported to occur in infants of diabetic mothers (IDMs). We report a newborn IDM with brachial artery thrombosis in utero and neonatal gangrene which necessitated a below elbow amputation at 5th day of life. The diagnosis of external left brachial artery thrombosis was made by Doppler sonography flow studies and was confirmed at autopsy. Despite the use of anticoagulants, the gangrene advanced and amputation of the necrotic forearm was performed. The postoperative period was complicated by mesenteric artery thrombosis with subsequent necrotizing enterocolitis, convulsions, septicemia and death. The reason for the increased tendency to develop thrombi in IDMs has not been elucidated. Changes in coagulation factors have been reported in newborn IDMs with poor control of maternal diabetes. Increased clotting and decreased fibrinolysis found in diabetics may lead to arterial thrombosis in IDMs in utero and postnatally. Use of anticoagulants in at-risk infants should be considered early to prevent further thrombosis and ischemic complications postnatally.

Key words: *arterial thrombosis in utero, newborn infant of a mother with diabetes mellitus, neonatal limb gangrene*

INTRODUCTION

Peripheral ischemia and gangrene presenting at birth is a rare clinical problem with a heterogeneous etiology and generally a poor outcome [4]. Although the association with maternal diabetes is significant [5], in most cases no identified cause has been found. The management of neonatal gangrene is usually conservative, preventing infection of the affected part and allowing the gangrenous portion to declare itself in order to optimize future reconstruction. In recent years,

death from this condition is rare, however when gangrene is established at birth, surgical amputation, autoamputation, or some loss of function is usual [9].

CASE REPORT

We report a 3250-gram female infant born at 34 weeks' gestation to a 24-year old gravida 2, para 1 mother who had a history of a large for gestational age infant, born at term without abnormality. The pregnancy was complicated by type 1 insulin – dependent diabetes of 1 year duration. The mother's hemoglobin A1c was measured throughout the pregnancy and ranged from 6.6 % to 7.1%. She was normotensive during the entire pregnancy. The amniotic liquid had normal volume and there was no premature rupture of the membranes.

The mother was screened for thrombophilia during the late gestation.

The thrombophilia investigations consisted of measurement of anticardiolipin IgG and IgM, total and free protein S antigen, antithrombin III activity, screening for factor V Leiden and prothrombin gene 20210A. All of them gave normal results.

The CTG showed evidence of foetal asphyxia and the infant was delivered by an emergent caesarean section. Apgar scores were 5 and 7 at 1 and 5 minutes, respectively. There were no signs of major trauma at birth.

Physical examination: The infant had a typical appearance of a diabetic fetopathy and a large for the gestational age weight – 3250 grams for a chronologic and morphologic maturation corresponding to 34 weeks gestation.

At delivery, it was noted that the infant was born with a malformed and hanging to the back left arm which had no active movements. The skin covering the arm distally from the middle of the brachium was swollen, cold, cyanotic and with large blisters. There were no arterial pulsations at the wrist. The surface of the left elbow was necrotic. The areas of deep skin, soft tissue and muscle necrosis enlarged in the next hours. The skin of the left palm was looking as "boiled" and its epidermis was peeling; gradually the gangrene spread diffusely on the whole left forearm with a defined demarcation line (fig.1).



Fig. 1. The second day



Fig. 2. The fifth day

The performed **Doppler sonography** flow study on the first day of life proved missing blood flow in the left a. brachialis externa and present flow in the left a. axillaris and a. brachialis profunda.

The patient underwent a below the elbow amputation on the 5th day of life.

On the first postoperative day the patient began having apneic episodes with desaturations and seizures. A **CT scan of the head** revealed a small intraventricular hemorrhage in the left brain ventricle without parenchym blood. There was no evidence of a sagittal sinus thrombus. Magnetic resonance confirmed these findings. No evidence of a thrombus could be identified in the renal veins or inferior vena cava by the **abdominal ultrasound**.

Pathologic examination confirmed ischaemic necrosis of the left antebrachium including skin, soft tissue, muscle, cartilage, and bone. The arteries were thick walled with varying amounts of intimal proliferation and/or recanalization consistent with previous thrombosis. There were also microscopic foci of dystrophic calcification in small vessels. The arterial changes may have occurred as recently as 2 weeks before delivery, i.e between 30 and 32 weeks' gestation. Besides, there were histological changes in the endocrine pancreas with hyperplasia of the islets commonly seen in infants born to diabetic mothers. There were also present changes of hyperlipidemia with abnormal storage of fat tissue paratracheally and in the intercostal muscles, and fat dystrophy in the parenchym organs. The lung was structurally immature with multiple atelectases and pneumothoraces. There was no histologic evidence of a renal vein thrombosis.

Laboratory tests showed elevated values of the immature white blood cells, suggestive of a neonatal infection: Metamyelocytes – 0.04; J- 0.02; St- 0.05, Sg- 0.43; Ly-0.19; Eo- 0.07; Mo- 0.20. The WBC were slightly elevated – $26 \times 10^9/L$ (normal $6 - 25 \times 10^9/L$). Platelet count was – $308 \times 10^9/L$ (normal $150 - 450 \times 10^9/L$); hemoglobin – 16.6 g/dl; hematocrit – 0.51; erythrocytes – $5.1 \times 10^9/L$ (normal $3.9 - 5.8 \times 10^9/L$) were in reference ranges for the gestational and chronologic age. C-reactive protein on the 24th hour of life was slightly elevated – 5.49 mg/l (normal, 0-5 mg/l).

Values of **time of bleeding** – 60 sec (normal 60-180 sec) and **time of clotting** – 180 sec (normal 360 – 480 sec) were decreased and value of **plasma thrombin time** – 17 sec (normal 16 – 27 sec) was within normal limits.

Blood and wound cultures were positive for Methicillin resistant *S. aureus*, confirming the neonatal bacterial infection.

Tracheal secretion, taken postoperatively from the endotracheal tube, was positive for *E. Coli*.

Management of the patient was initially directed to treatment of the developing bacterial infection, thrombolytic therapy with high doses of anticoagulants, local antibacterial treatment and dressings of the gangrenous portion of the limb, and supportive infusions with fluids and electrolytes.

The antibacterial treatment started with Cefotaxime, Amikacin and Flagyl. Systemic heparinization (300U/ kg per body weight) was combined with Trental (20 mg/kg/ 24 hr). Sterile dressings with Bactigrass and surgical cleaning of the necrotic surface were done twice daily till the operation.

On the 5th day of life the infant was transferred to the Pediatric Surgery and an **amputation at the level of the middle of the left brachium** was performed.

The antibacterial, anticoagulant and supportive cardio-respiratory management was continued. Transfusion therapy and anticonvulsive agents were added.

Nevertheless, the state of the patient deteriorated postoperatively by meningoencephalitis, necrotising enterocolitis and by multiple pneumothoraces.

She could not be weaned from the respirator and expired on the 19th day of life.

DISCUSSION

The increased incidence of thrombosis in infants of diabetic mothers has been well recognized. In the majority of previously reported cases, a renal vein thrombus served as the source of embolization. Emboli dislodged from the renal vein or inferior vena cava are carried through the venous circulation to the right atrium. These emboli progress through the foramen ovale into the left side of the heart and ascending aorta. Before birth, blood flow from this source preferentially supplies the head and upper extremities. Therefore, most reports of extremity gangrene in IDMs presenting at birth, have involved embolization from the renal vein to the upper extremities [1, 3, 6, 11].

In contrast, the patient reported here had gangrene of the upper limb without an associated renal vein thrombus. There are two other reports of IDMs who presented at birth with a clinical examination consistent with occlusion of the brachial artery in the first case [10] and of the femoral artery in the second report without an associated venous thrombus [8]. Thrombi from the placenta may be the source of emboli in those IDM patients without associated renal vein thrombi.

In a clinicopathologic correlation analyzing the association between placental thrombi and somatic thrombi in the fetus, autopsy findings demonstrated that 37.5% of fetuses with significant placental thrombi had associated somatic thrombi [7]. The fetal lesions were found in the brain, lungs, and kidneys.

In our case, unfortunately the placenta was discarded before the pathology review.

The patient reported here was born with septicemia which additionally contributed to the development of the thrombotic process and complicated the clinical state of the infant postnatally. Extremity gangrene in neonate born to diabetic and nondiabetic women has been attributed to certain complications of pregnancy and delivery as prolonged rupture of membranes and intraamniotic infection, prolapse of the affected limb between the head and uterine wall, or a "dry" difficult labour. In

this case, there were no evidences of trauma at birth and before the delivery. The patient was distinctive in the timing of the vascular occlusion. The pathologist consulted about the amputated limb in this infant indicated that the occlusion most likely occurred between 30 and 32 weeks' gestation. Approximately half of the cases present on the first day of life [5], but only one of them presented with evidence of prolonged in utero thrombosis [8].

Although the majority of reported neonates with early peripheral ischemia have been IDMs, the mechanism for their propensity to form thrombi has not been established. The development of thrombosis within the vasculature depends on the balance between procoagulant and antithrombotic factors and between activators and inhibitors of fibrinolysis. Fibrinolysis is mediated by plasmin, the enzymatically active form of plasminogen. Plasminogen is converted to plasmin by tissue plasminogen activator and urokinase plasminogen activator.

In a previous report of an IDM with multiple vascular thrombi, the plasminogen activity was shown to be significantly less than the lower 95th percentile confidence limit for the appropriate gestational and postnatal age [8].

All neonates have decreased plasminogen activity compared with normal adults. Perhaps in the IDMs reported with arterial occlusion the deficiency of the plasminogen activity was sufficient to result in thrombi formation.

In this case, we made a work up to evaluate the infant's coagulation by the routine investigations of the lab. The time of clotting was significantly decreased than the normal for the gestational and chronologic age and the time of bleeding was on the lower reference limit. Their values reflected the deficient fibrinolysis of the patient.

A possible risk factor for thrombus formation in the baby is the maternal thrombophilia. Maternal anticardiolipin antibodies are associated with venous or arterial thrombosis in the mother, preeclampsia, intrauterine growth retardation, and fetal death. In this case report, neither the mother nor the infant had features commonly seen in anticardiolipin syndrome. The mother was not hypertensive during the pregnancy and the infant did not have evidence of in utero growth retardation. Maternal anticardiolipin antibodies generally predispose the mother to thrombosis and do not result in fetal or neonatal thrombosis. The proposed mechanism for thrombus formation is that anticardiolipin binds to phospholipids on the platelet surface causing platelet agglutination that is followed by fibrin formation [12]. The complications in the fetus are related to placental vessel thrombosis. There is one case report of thrombosis in a neonate whose mother had anticardiolipin antibodies. The infant had thrombi in the renal vein and inferior vena cava. In that case, there was a 2-year history of maternal lupus, positive antinuclear antibody, a high titer of maternal anticardiolipin IgG and a moderate level of neonatal anticardiolipin IgG [2]. In the infant reported here, the maternal IgG and Ig M titers to cardiolipin were negative and the mother's factor V Leiden and prothrombin gene were negative too.

To our knowledge, IDMs with thrombi and associated ischemic changes had minimal clotting studies done postnatally. Assays looking for abnormalities in clot formation and fibrinolysis would be very informative in subsequent IDMs with neonatal thrombosis. They may contribute substantially to the adequate treatment of the coagulation disorder based on recombinant tissue plasminogen activators.

In addition, any infant who presents with a thrombus that occurred in utero or shortly after delivery should have a pathologic exam of the placenta. From this case report and two others, it is evident that not all IDMs with thrombi have an associated renal vein thrombus that serves as a source of systemic emboli.

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