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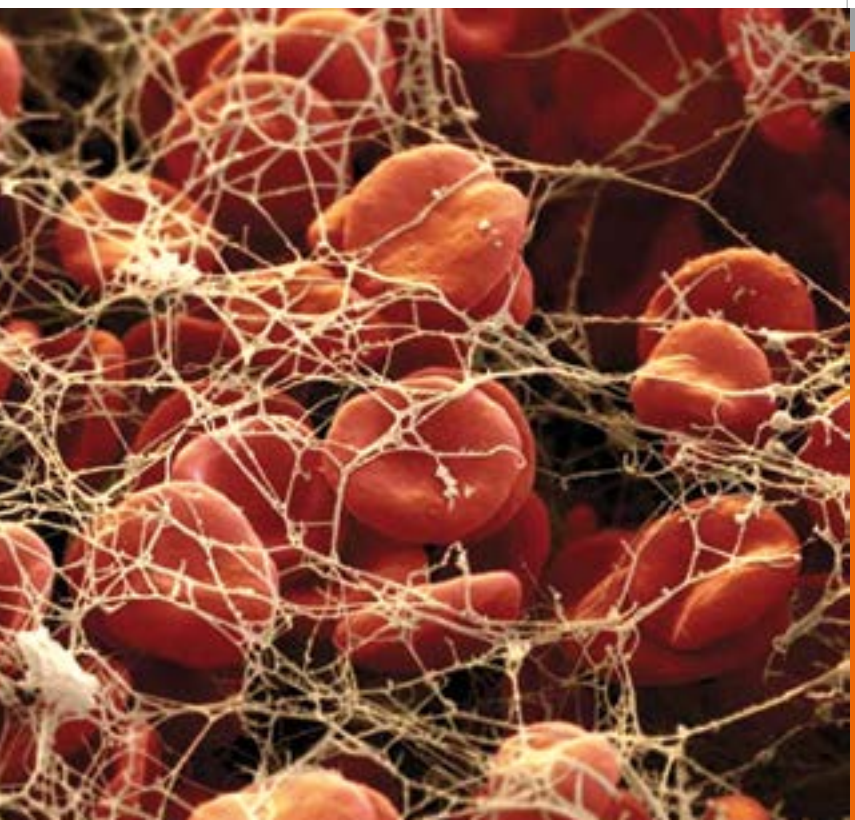
Fatal pulmonary embolism in a premature neonate after twin-twin transfusion syndrome



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INTRODUCTION

While pulmonary embolism (PE) represents a frequent emergency in adults, PE occurs very rarely in the pediatric age group (1). However, it is increasingly being recognized that thrombotic disease may frequently be under diagnosed (2). The incidence of thromboembolic events in children is highest during the neonatal period (3), which is characterised by a delicate equilibrium of pro- versus anticoagulant factors. Over the past years, thrombotic complications in newborns have received broader attention (4), in part thanks to improved diagnostic procedures. We present a case of a premature infant with fatal PE.

CASE REPORT

A premature baby girl weighing 1400 grams was born at 29 weeks of gestation by caesarean section because of maternal chorioamnionitis. The monozygotic twin pregnancy had been complicated by twin-to-twin transfusion syndrome (TTTS) with the girl presented here being the recipient. The baby was intubated for respiratory distress syndrome after birth and umbilical venous and arterial lines were placed. The umbilical artery line was immediately removed following the x-ray as the tip was malpositioned in the iliac artery. CBC on admission showed borderline polycythemia (hemoglobin 202 g/l, hematocrit 58%) and a normal platelet count (320x109/l). After receiving porcine surfactant (Curosurf®) for radiologically evident hyaline membrane disease, the infant was extubated and did well on room air without additional respiratory assistance. The umbilical venous catheter

was removed on day three, and peripheral catheters on day nine when full enteral feeds were reached.

At 10 days of age, the baby started requiring supplemental oxygen (25-30%). Radiologially, patchy pulmonary markings were noted and interpreted as early manifestation of bronchopulmonary dysplasia (Fig. 1). Therefore, diuretic therapy with spironolactone and hydrochlorothiazide was initiated with no clear improvement. Arterial blood pressure and electrolytes, including calcium, were always within normal range.

On day 14 of life, directly following capillary heel stick blood sampling, the ipsilateral leg became pale and cooler with no peripheral pulses palpable. The baby was otherwise well, and showed no other signs of compromised perfusion. Within an hour, the perfusion of the right leg normalized spontaneously. Duplex sonography of the abdominal, pelvic and lower extremity vessels excluded arterial or venous thromboses, including renal vein thrombosis. In order to rule out a cardiac origin of a possible thromboembolic event, echocardiography was performed. There was no evidence of congenital heart disease, pulmonary hypertension or thrombotic disease. Given the spontaneous rapid resolution and the normal radiographic findings, arterial vasospasm triggered by the painful stimulus was diagnosed.

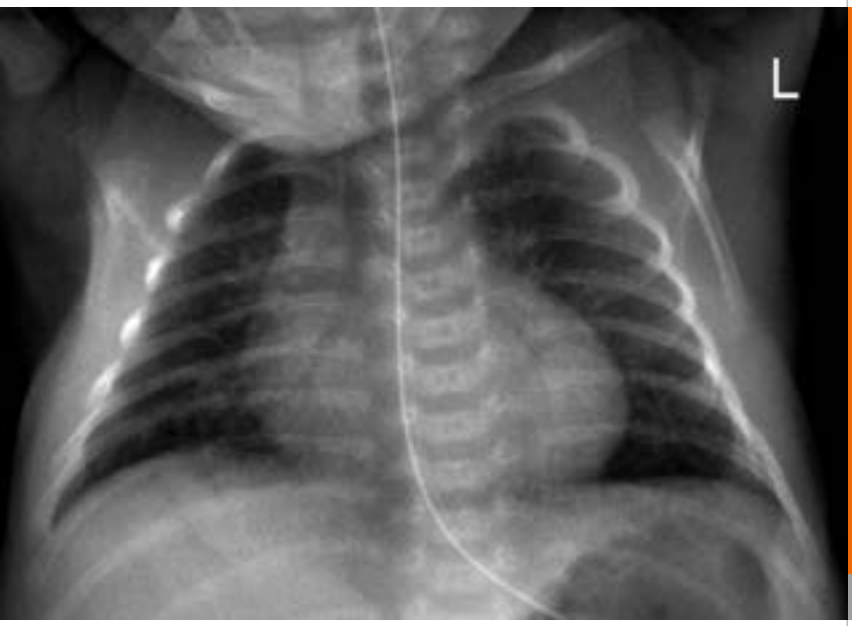

Fig. 1

Chest x-ray on day 10 showing increased pulmonary markings.

On day 20 of life, while lying comfortably in bed, the baby became acutely cyanotic with oxygen saturations around 60%, and manifested respiratory distress with tachypnea and subcostal retractions. Blood pressure was 42/22 mmHg (mean 30 mmHg) with a heart rate of 184 bpm. There was no improvement in oxygenation with 100% oxygen. She was intubated and mechanically ventilated. Emergency thoracocentesis of both pleural spaces ruled out a tension pneumothorax. Dopamine was started to treat arterial hypotension. On the CXR, diminished pulmonary vasculature was noted. Echocardiography showed suprasystemic pulmonary arterial pressure with severe tricuspid regurgitation, a flattened interventricular septum, right-sided ventricular dilatation with almost no flow across the pulmonary arteries, and right-to-left shunting across the foramen ovale. There was severe lactic acidosis (pH 6.8, lactate 14.8 mmol/l). In spite of maximal intensive care support with catecholamines, high-frequency oscillatory ventilation and inhaled nitric oxide, the baby further deteriorated and died approximately 2 hours after the onset of the sudden event.

At autopsy, large emboli were found extending into both pulmonary arteries (Fig. 2). The right lower lobe showed a large area of infarction (Fig. 3). Microscopic examination revealed several peripheral pulmonary artery emboli (Fig. 4) and several extensively calcified renal vein thromboses (RVT) (Fig. 5). Due to the high degree of calcification and signs of beginning thrombus

organisation, the age of the RVT was estimated to be >1 week, in contrast to the more recent, smaller pulmonary artery emboli estimated to be aged several days. A renal origin of the PEs was thought probable.

Family history revealed that the maternal grandfather had experienced PE at the age of 78 years. Extensive thrombophilia screening was performed with DNA of the deceased baby, her surviving monozygotic twin sister and the parents. Coagulation studies including Protein C and S levels, antithrombin III, homocystein concentration, and antiphospholipid antibodies were negative. Genetic screening for factor V Leiden (R506Q) and prothrombin mutation (20210G>A) and methylene-tetrahydrafolate reductase variant (C677T) was negative.

Apart from intubation and ventilation for hyaline membrane disease, the surviving twin (birth weight 1245 gram, hemoglobin 112 g/l, hematocrit 33% on admission), had an uneventful course. Echocardiography and abdominal Doppler studies were normal.

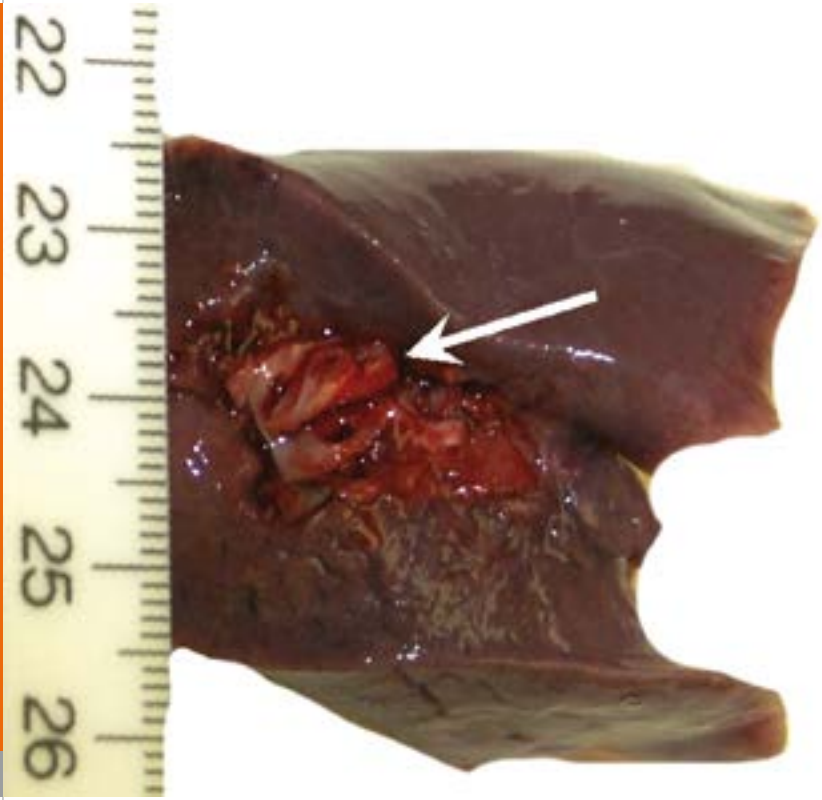

Fig. 2

Post-mortem specimen of the right lung with opened main pulmonary artery showing a large embolus (arrow).

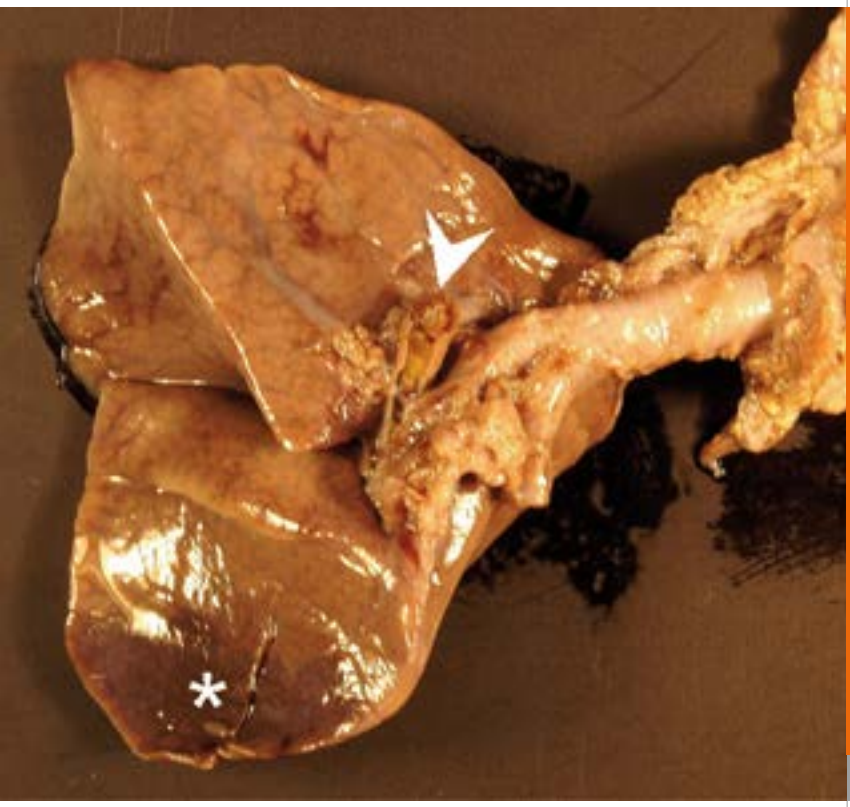

Fig. 3

Post-mortem specimen showing bilateral pulmonary emboli (arrowhead) and infarction in the right lower lobe (asterisk).

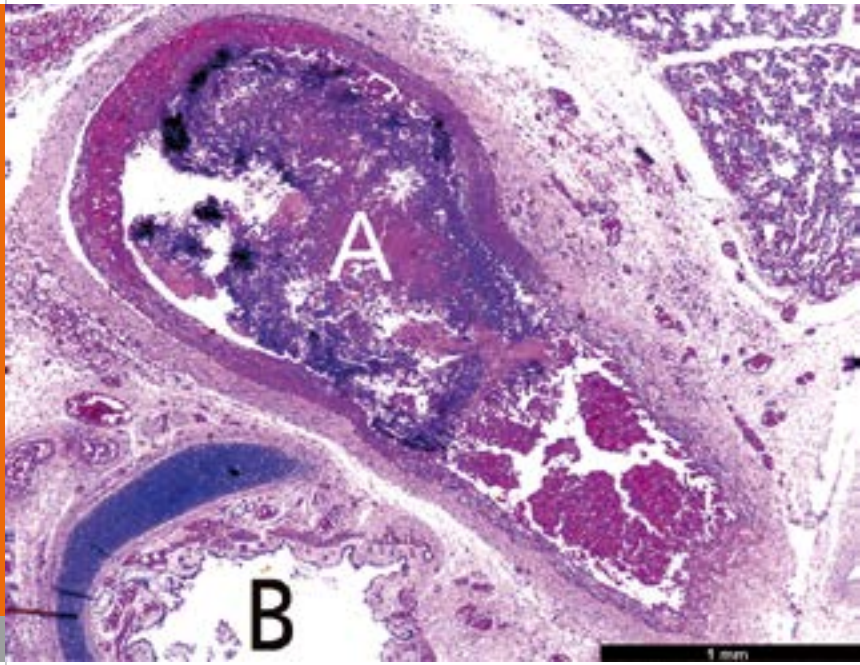

Fig. 4

Post-mortem histology of the pulmonary vascular bed showing a pulmonary embolus (A: artery, B: bronchus).

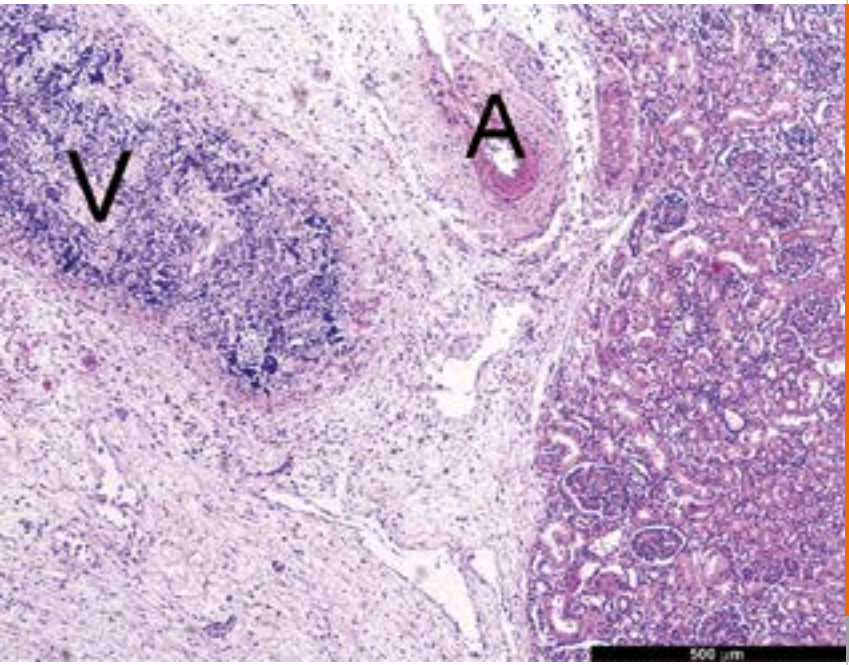

Fig. 5

Post-mortem histology of the kidney showing a calcified renal vein thrombosis (V: vein with thrombus, A: artery).

DISCUSSION

To the best of our knowledge, this is the first case report on a fatal PE in a premature infant. In the absence of inherited thrombophilia and disseminated intravascular coagulation, the extensive renal and pulmonary thromboses were thought to have arisen either in relation to the umbilical venous catheter or as an indirect consequence of TTTS. We assume that the combination of polycythemia, prematurity and other triggers such as diminished intravascular volume due to diuretics, may have further propagated the fatal thrombotic event. Recipient twins may be at particular risk due to chronic hyperviscosity associated with polycythemia and thrombocytosis (5). TTTS was shown to be an independent risk factor in a study on neonatal ischemic stroke (6).

In contrast to adults where PE represents a frequent cardiovascular emergency, the condition is exceedingly rare in children. A prospective Dutch registry in children aged 0 to 18 years has reported an incidence of 0.14 per 10 0000 children (1). However, the true incidence of PE in the pediatric population is probably underestimated. In neonates, several case reports on PE have been published (7-11) usually describing term infants with persistent pulmonary hypertension of the newborn or severe respiratory failure. Presentation of PE may range from mild respiratory distress to severe pulmonary hypertension and acute right-sided heart failure leading to severe hypoxemia and death (12). Diagnosis of PE in infants is difficult, since experience

with ventilation-perfusion lung scanning and spiral computed tomography is limited in this age group, while pulmonary angiography is invasive (11). Consequently, most cases are diagnosed either by echocardiography or during the post-mortem examination (10, 13). Smaller PEs may frequently be missed or misinterpreted as respiratory diseases such as pneumonia or pulmonary edema. In our case, moderate hypoxemia probably caused by smaller PEs was mistaken as an early sign of bronchopulmonary dysplasia.

RVT is the most common non-catheter related thrombosis in neonates, occurring in 0.5/1000 neonatal intensive care unit admissions and accounting for 20% of neonatal thrombotic events (2, 3). Classic symptoms are hematuria, palpable abdominal mass, thrombocytopenia and frequently arterial hypertension, but only a minority of patients present with the complete triad (4). The recent review by Lau et al. confirmed that RVT occurs frequently in the absence of prothrombotic risk factors (4). Doppler ultrasound studies of the renal vessels is considered gold standard for diagnosis of RVT and advances in radiologic technique have improved diagnostic accuracy over recent years.

Within the pediatric population, neonates are at the greatest risk for venous thromboembolism (5.1/100 000 live births per year), with a second peak in incidence during puberty and adolescence (14). The risk

factors differ between neonates and older children, with sepsis or necrotising enterocolitis, dehydration or hypovolemia, maternal diabetes, asphyxia, congenital heart disease and central venous catheters being the most frequent clinical risk factors in neonates (2). Although vitamin-K-dependent procoagulant clotting factors are decreased in neonates, particularly if born preterm, coagulation inhibitor concentrations are significantly lower compared to adults as well (3). In addition, levels and activity of both pro- and anticoagulant factors undergo significant changes during the neonatal period. This delicate and dynamic equilibrium between coagulation and fibrinolysis is easily disturbed by perinatal or iatrogenic factors. In the presented case, no inherited cause of thrombophlia was found. A recent meta-analysis by Young et al. showed that inherited deficiencies of the natural anticoagulants protein C, protein S, and antithrombin are present in less than 10% of pediatric patients with venous thromboembolism (14).

In conclusion, the present case illustrates that both renal and smaller pulmonary thromboses may progress asymptomatically. The incidence of PE and of RVT may therefore be underestimated. Considering the potentially lethal course of PE, pediatricians and neonatologists should maintain a high degree of suspicion for thrombotic events in infants with sudden deterioration of oxygenation, acute signs of respiratory distress or unexplained pulmonary hypertension.

ACKNOWLEDGEMENT

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