Intra-cardiac thrombus in a preterm infant: a management conundrum

A case of a large intra-cardiac thrombosis in an extremely low birthweight preterm infant is presented. This thrombus was detected during an echocardiogram following a positive blood culture and a positive umbilical venous catheter tip culture. Striking a balance between reducing the risk factors for thrombosis versus the requirement for parenteral nutrition and central infusions through indwelling catheters in preterm infants is challenging. This case demonstrates the complexity of diagnosing and managing thrombosis in an extremely low birthweight preterm infant.

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Key points

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1. An intra-cardiac thrombus occurred in a newborn infant leading to management difficulties.
2. The risk factors for thrombus are reviewed.
3. Prevention through consideration of all predisposing factors is imperative.

The case report

A female infant was born prematurely at 29 weeks' gestation weighing 568g. She was delivered by emergency caesarean section for intrauterine growth restriction, reversed end-diastolic flow and non-reassuring cardiotocograph. She required surfactant and initial ventilation. She was extubated to non-invasive ventilation by seven hours of age. Umbilical venous (UVC) and arterial (UAC) catheters were sited on day one. The UVC tip was seen on X-ray at T8/9 thoracic spine level and at the border of the heart, thus was pulled back and a repeat X-ray identified it at the T12 level.

On day five, the infant developed a distended abdomen with feed intolerance and bilious aspirates. Following this development, she was placed nil by mouth, underwent a septic screen and was started on antibiotics for suspected necrotising enterocolitis without X-ray changes. Coagulase-negative *Staphylococcus epidermidis* (CoNS) was detected on blood culture on day six. Following the positive blood culture the UVC was removed on day seven; subsequently, the catheter tip was found to be colonised with CoNS. A central venous catheter (CVC) was sited to deliver parenteral nutrition. A repeat blood culture on day nine was positive for CoNS. The infant was severely thrombocytopenic secondary to sepsis and required repeated platelet infusions.

An echocardiogram was performed on day 18 to look for evidence of infective endocarditis given the persistently positive blood cultures, the raised C-reactive protein (CRP) and thrombocytopenia. The echocardiogram demonstrated a large (12.6 x 5.4mm) vegetation in the right atrium and oscillating near the orifice of the tricuspid valve but not attached to the valve apparatus (**FIGURE 1**).

The superior vena cava flow was unobstructed but the inferior vena cava flow to the heart looked narrower than normal. Cardiologists from the regional cardiac centre advised treatment with antibiotics and observation, due to the patient's gestation, size and thrombocytopenia. The infant commenced vancomycin, meropenem and rifampicin as per the microbiologists' guidance. On day 19 the infant became critically unwell secondary to sepsis, cardiac failure and bilateral pleural effusions. High-frequency oscillatory ventilation (HFOV) was required alongside inotropic support. A discussion with the family was made regarding withdrawal of care given the severity of the infant's condition. The baby did, however, improve following this stormy period and intensive care support was stepped down gradually. On day 34, repeat echocardiography demonstrated a reduction in the size of the vegetation to 7.6 x 3.8mm, which looked more echogenic. The inferior vena cava was partially occluded and it was clear that this vegetation was arising from the inferior vena cava and extending through the right atrium and protruding slightly into the left atrium through a patent foramen ovale (**FIGURES 2 AND 3**).

The regional cardiac centre advised starting low molecular weight heparin, given the higher risk of embolism versus the perceived lower risk of intraventricular haemorrhage (IVH) due to advanced gestation and resolved thrombocytopenia. Low molecular weight heparin (enoxaparin) was started by subcutaneous injection at a low dose of 1mg/kg twice daily due to hepatic impairment (conjugated hyperbilirubinaemia). This raised practical difficulties due to the infant's size at that time (800g with limited subcutaneous tissue), therefore a special dilution was needed to give the smallest volume for injection possible. The enoxaparin dose was increased to achieve an anti-factor Xa within the target range (between 0.5 and 1.0IU/mL). The infant's inflammatory markers normalised and the antibiotic course was stopped after eight weeks.

On subsequent echocardiograms, the thrombus appeared smaller in size. The infant was started on an anti-platelet dose of oral aspirin and the enoxaparin was stopped. The infant was transferred to the surgical centre for abdominal distension, which improved after rectal washouts (suspected meconium plugging and preterm gut dysmotility). The infant was discharged home from there. A further heart scan in the follow-up clinic at five months of age showed a tiny residual thrombus in the right atrium attached to the atrial septum, and clearing of the inferior vena cava obstruction.

Discussion

The incidence of symptomatic thrombosis is reported as 2.4 per 1,000 neonatal intensive care unit admissions[1] and 5.1 per 100,000 live births.[2] Widespread use of umbilical and central venous lines in neonatal intensive care remains the most important risk factor for thrombosis in newborn infants. Preterm infants *in extremis* are at a higher risk for thrombosis. Recent estimates of UVC related thromboses range from 13% in clinical studies to 20-65% on autopsy.[3] It has been reported that 90% of all thromboembolic events on the neonatal unit were due to vascular access devices.[4] There are, however, no reported incidence data in the literature for intra-cardiac thrombosis in newborn infants associated with CVCs. In this case, a UVC was required for parenteral nutrition as the infant had several risk factors for necrotising enterocolitis, including extremely low birth weight, preterm birth and reversed end diastolic flow. It was estimated that of newborn infants with portal vein thrombosis, 73% had a history of UVC placement.[5] The sites of venous

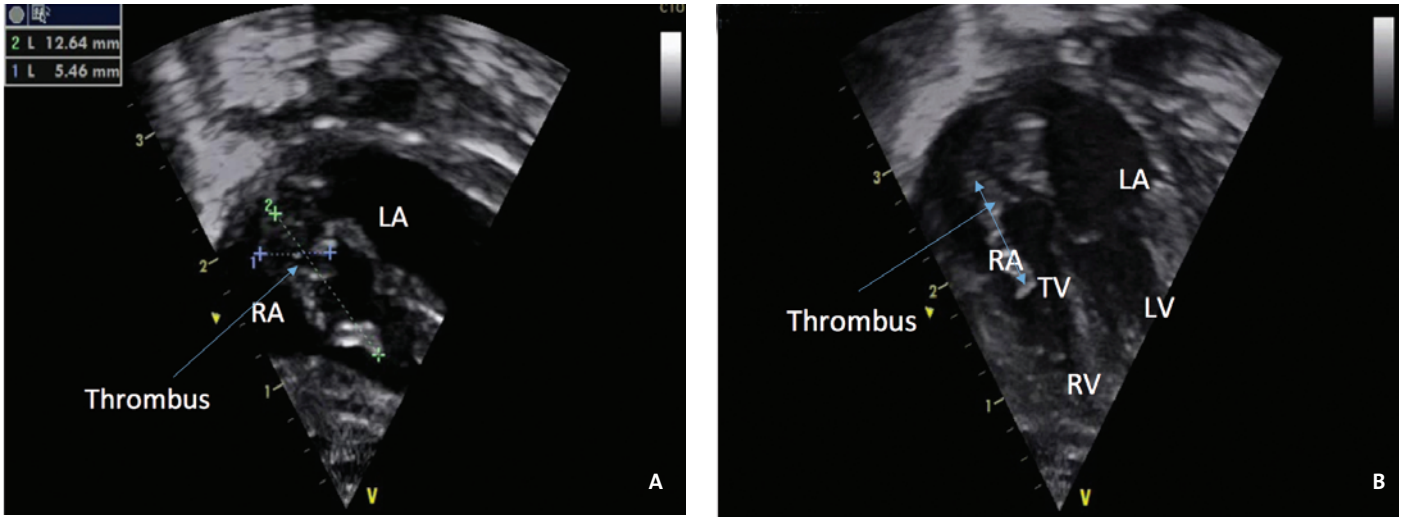

FIGURE 1 Echocardiograms on day 18. (A) Subcostal view, and (B) four-chamber view, showing a large thrombus (arrows) in the right atrium (RA) attached to the atrial septum and extending through the orifice of the tricuspid valve (TV).

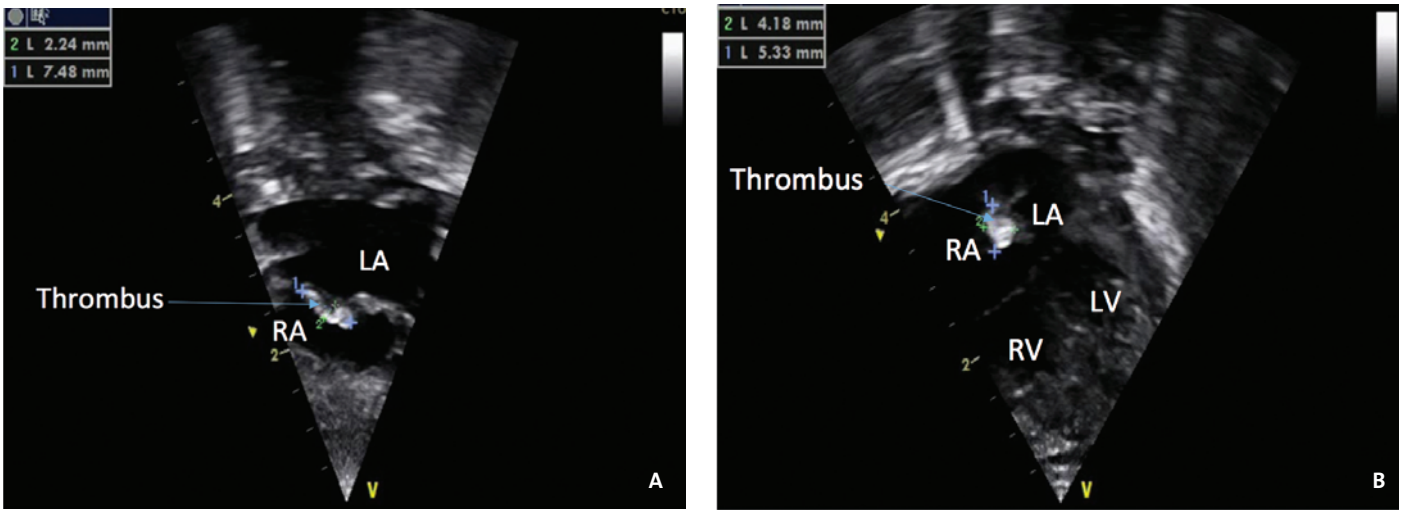

FIGURE 2 Echocardiograms showing reduction in the size of the thrombus at the time of discharge. (A) Subcostal view, and (B) four-chamber view.

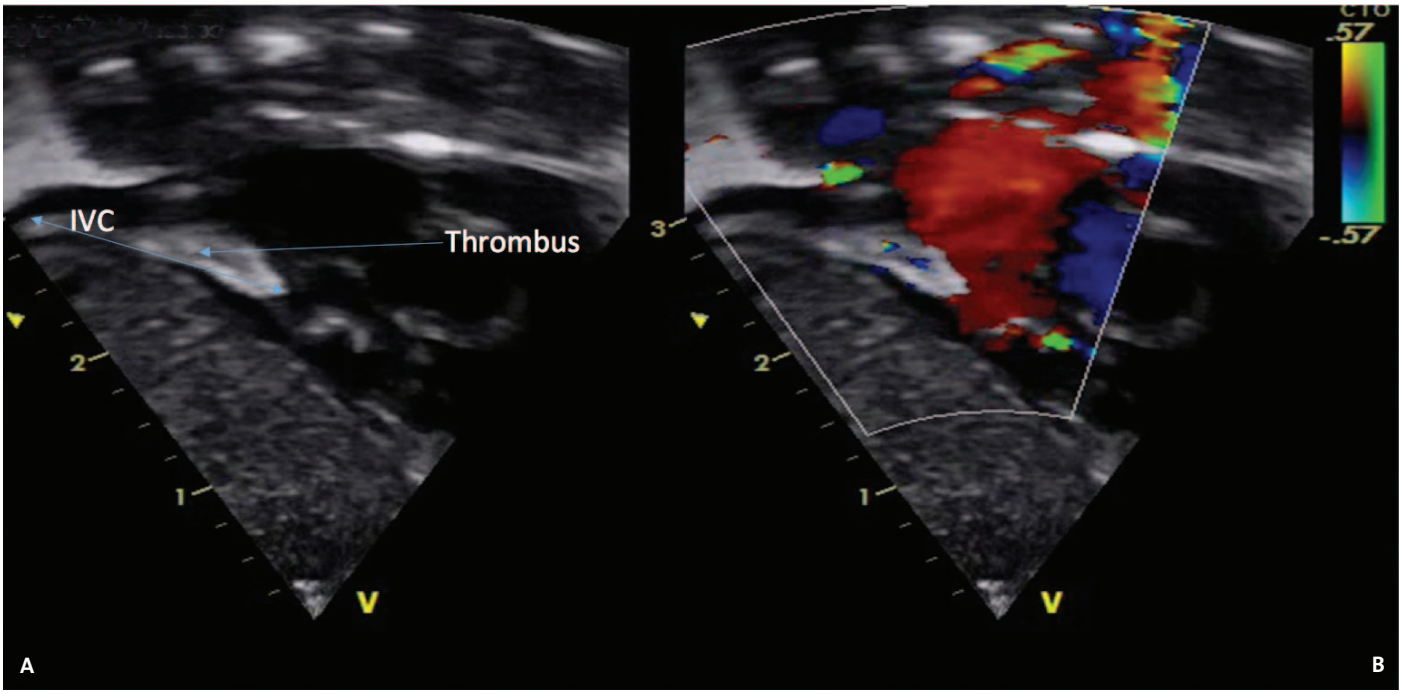

FIGURE 3 (A) An echocardiogram (subcostal view) showing the thrombus possibly originating from the inferior vena cava (IVC) and (B) partial obstruction of the IVC due to the thrombus.

thromboses can be variable but are often located in the renal vein, portal vein, inferior and superior vena cava and right atrium.[1] In the case presented here, extension of the thrombus from the inferior vena cava into the right atrium and absence of a congenital heart disease might suggest a thrombus originating from the UVC.

Several other *in vivo* risk factors contribute to the development of thromboembolism in the critically ill newborn infant. These include:

- infection and inflammation
- disseminated intravascular coagulation
- impaired liver function
- congenital heart disease.

The haemostasis system is developing throughout infancy, with reduced coagulation factors and thrombolytic system activities. Infants have a high haematocrit with contracted intravascular volume in the first few days of life therefore increasing their risk of thrombosis. Newborn infants with sepsis develop an acquired pro-thrombotic state due to increased consumption of already limited supplies of coagulation inhibitors. Indwelling catheters are large compared to the diameter of the vessel and can obstruct up to 50% of the lumen.[6]

Although using central catheters cannot be completely avoided, strict guidelines and care bundle interventions may reduce the incidence of catheter-related complications including thrombosis. This is clearly explained in the recommendation from the British Association of Perinatal Medicine (BAPM) framework for the practice for use of CVCs in newborn infants.[7]

Thromboses in preterm infants can be difficult to recognise and are normally identified incidentally. Persistently positive blood cultures with suspicious organisms in a preterm infant with an indwelling catheter are suspicious of infective endocarditis. An echocardiogram could help in identifying the source and the extent of the vegetation or thrombus, as in the case presented here. Without an echocardiogram, this complication may be unrecognised and even become fatal.

Vancomycin is considered as first choice in treating infective endocarditis (or infected thrombus) associated with CoNS. In this case, the repeat blood culture was still positive, prompting the addition of rifampicin. An eight-week course of both antibiotics helped to eradicate the organism. Gombert et al showed that in patients with CoNS, the addition of rifampicin to vancomycin resulted in enhanced bactericidal activity against all isolates when compared to either antibiotic alone.[8] The largest study supporting the use of rifampicin combination therapy for prosthetic valve endocarditis showed that 21 out of 26 patients with methicillin-resistant *S. epidermidis* infection were successfully cured with the rifampicin-vancomycin combination.[9]

Several therapeutic options for the acute management of thrombosis and thromboembolism are available, including simple observation, anticoagulation (eg unfractionated or low molecular weight heparin, anti-platelet agents, etc), thrombolytic therapy (eg tissue plasminogen activator) or surgical interventions (eg thrombectomy). However, in low birthweight, preterm infants with a high risk of IVH the options are limited. Management needs to be individualised and risks weighed against benefits in each instance. In this case, the option of surgery was not available due to the size of the infant. Thrombolytic therapy was not considered as it is contraindicated in preterm babies less than 32 weeks' gestation due to concerns over major bleeding such as IVH and may not be optimally effective due to physiologically lower levels of plasminogen in newborn infants.[10]

Anticoagulation was not initially considered in this infant because of disseminated intravascular coagulation. Contraindications for anticoagulant therapy include thrombocytopenia with platelet counts of $<50x10^9$/L and a history of high grade IVH. However, with time, the risk of embolisation, obstruction to the inferior vena cava and the potential to extend to the valve outweighed that of haemorrhage from therapeutic interventions. Mortality

rates are highest for those with aortic line- (thromboembolism to the brain) or CVC-associated thromboses, involving either the right atrium or the superior vena cava,[2] due to the risk of dissemination of emboli into the lungs or obstruction of the pulmonary artery.[11]

Having made the decision to start anticoagulation, the next consideration was how best to deliver it. The use of enoxaparin in 12 preterm and four term infants showed resolution of thrombus in 71% of the patients with no serious adverse events reported.[12] Low molecular weight heparin has more predictable pharmacokinetics (therefore needing less frequent monitoring) and fewer complications compared to continuous infusion of unfractionated heparin, which requires a CVC (posing further infection risk) and multiple blood tests (with the risk of a blood transfusion). Low molecular weight heparin given subcutaneously twice daily was not without difficulty as the infant had limited subcutaneous tissue available. The dilution was complicated in order to reduce the volume being administered. There were no local or neonatal network guidelines available for a recommended dosage of enoxaparin, therefore guidance was taken from the regional children's hospital specialists. Higher doses of 2mg/kg twice daily were needed in this infant to achieve an anti-factor Xa level within the target range (0.5 to 1.0).[13]

Administration of low molecular weight heparin by the parents and monitoring at home is not feasible. As the infant matured and the platelet count recovered, changing to an anti-platelet agent (aspirin) seemed the better option.

Conclusions

An intra-cardiac thrombus can occur in a newborn infant. Since management is so complex in these patients, the emphasis is on prevention of thrombus formation. As such, it is vital that the insertion of invasive catheters is carefully balanced against clinical need and a good practice framework. It is important to be aware of this complication related to CVCs and to consider an echocardiogram in appropriate cases, especially with persistently positive blood cultures, persistent thrombocytopenia and persistently elevated CRP, despite antibiotic treatment. Treatment needs to be individualised, however low molecular weight heparin is the safest option in preterm infants (**FIGURE 4**).

- Sick preterm infants are at higher risk for a thrombosis, commonly due to vascular access devices
- Strict guidelines and care bundle interventions may reduce catheter-related complications, including thromboses
- Vancomycin combined with rifampicin resulted in enhanced bactericidal activity for CoNS-associated infective endocarditis
- Thrombolytic therapy should be avoided in sick preterm infants
- Low molecular weight heparin may be a better option until the infant is ready for anti-platelet therapy

FIGURE 4 Important lessons learned from this case.

Patient consent

The authors received written consent to publish this report from the patient's parents.

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