Case Report

Infective Endocarditis due to Unusual Pathogens Complicated with Pulmonary Thromboembolism: A Rare Occurrence in a Premature Infant

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Abstract

Background: Survival of low birth weight preterm neonates has increased with the availability of better neonatal care, however, the use of central lines for longer duration increases the risk of bacterial and fungal sepsis. Neonatal infective endocarditis (IE) is a rare presentation of neonatal sepsis and is often associated with complications and high mortality. **Clinical Description:** A 36 weeker, premature baby, hospitalized for early onset sepsis, was transferred to our hospital on day 15 of life, with an umbilical catheter in situ, with fever, respiratory distress, and persistent thrombocytopenia. Clinical examination revealed decreased oxygen saturation, crepitations in the right lung field, systolic murmur, and hepatomegaly. **Management and Outcome:** Baseline investigations revealed positive septic screen with thrombocytopenia with meningitis, neonatal cholestasis, and right sided consolidation on chest X ray. A two dimensional echocardiography (ECHO) revealed vegetation on the tricuspid valve, and blood culture from two sites revealed growth of *Candida tropicalis* and *Serratia marcescens*. Colistin, tigecycline, and amphotericin B therapy were initiated as per sensitivity along with low molecular weight heparin for prevention of embolization. The baby developed acute worsening in respiratory distress after 4 weeks of therapy. Repeat ECHO revealed increased size of cardiac vegetation and computed tomography of thorax with pulmonary angiography revealed pulmonary thromboembolism. Unfortunately, the baby succumbed to complications of IE. **Conclusion:** Invasive instrumentations such as umbilical catheterization and prolonged hospitalizations of premature newborns predispose them to develop IE, especially with unusual organisms. Such infections have a complicated course and may be fatal.

Keywords: Fungi, *Serratia*, tricuspid valve, umbilical catheterization, vegetation

Infective endocarditis (IE) has rarely been reported in neonates, with fungal etiology being extremely uncommon.[1] With increasing survival of neonates and use of invasive devices and prolonged hospitalization, such complications are rising in this population, with high mortality.[2] We discuss a case of premature neonate with tricuspid valve IE, due to unusual organisms and its complications.

Clinical Description

A male preterm baby of 36 weeks' gestational age was referred to our center on day 15 of life with a diagnosis of clinical sepsis and thrombocytopenia. The baby was the first-born child of nonconsanguineously married parents, delivered by Cesarean section for meconium-stained liquor with fetal distress, at a local hospital, and cried immediately after birth. Mother was a booked primigravida with an uneventful antenatal period. However, her antenatal ultrasound reports and Doppler study were unavailable. The baby developed respiratory distress by 2 hours of birth and was started on noninvasive ventilation. On starting minimal enteral nutrition by orogastric tube on day 2 of life, the baby developed feed intolerance and thus feeds were withdrawn was started on intravenous fluids along with cefotaxime and gentamicin through umbilical venous catheter. Antibiotics were upgraded to meropenem, vancomycin, and fluconazole on day 5 of life in view of persistent respiratory distress and worsening thrombocytopenia. The baby was administered nine units of platelets for thrombocytopenia. The blood culture was sterile. As there was no improvement in thrombocytopenia, the child was referred to our center on day 15 of life.

On arrival in our hospital, the baby was lethargic, febrile, and tachypneic with a respiratory rate of 70/minute (Downe

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Quick Response Code:

Website: www.ipcares.org

DOI: 10.4103/ipcares.ipcares_208_23

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Submitted: 29-Sep-2023 **Revised:** 28-Mar-2024
Accepted: 31-Mar-2024 **Published:** 13-May-2024

How to cite this article: Patra S, Patwal P, Chetan C, Gupta G. Infective endocarditis due to unusual pathogens complicated with pulmonary thromboembolism: A rare occurrence in a premature infant. Indian Pediatr Case Rep 2024;4:114-7.

score of 3/10), SpO_2 of 85% on room air, heart rate of 150/minute with a capillary filling time of 3 seconds, and blood pressure of 68/36 (mean arterial pressure: 42) mmHg. The baby weighed 1400 g (small for gestational age), length of 40 cm, head circumference of 31 cm, and ponderal index of 2.18 suggestive of severe symmetric fetal growth restriction. The baby was icteric but had no pallor, cyanosis, or edema. Chest examination revealed crepitations on the right side, while cardiovascular system examination revealed a short systolic grade 2/6 murmur best heard in the left upper sternal border. Abdominal examination revealed hepatomegaly with a liver span of 8 cm. The umbilical venous catheter, which was *in situ*, was removed at admission as it was in place for more than 2 weeks and was visibly soiled. Based on the clinical presentation and examination, provisional diagnosis of clinical sepsis with pneumonia with neonatal jaundice in a growth-restricted newborn, was considered.

Management and Outcome

The child was admitted in the neonatal intensive care unit and was started on supportive management with a heated, humidified, high-flow nasal cannula (HHHFNC) with flow of 5 L/minute and FiO_2 30% along with intravenous fluids, not requiring any vasopressor support. Investigations revealed a positive sepsis screen with an absolute neutrophil count of 2200/mm^3, platelet counts of 18,000/mm^3, C-reactive protein of 39 mg/l, and hyperbilirubinemia [Table 1]. The chest X-ray was suggestive of consolidation without cardiomegaly. The baby being hemodynamically stable on HHHFNC, lumbar puncture was done under cover of platelet transfusion, which revealed meningitis. Neurosonogram was normal. Meropenem, vancomycin, and fluconazole were continued in anti-meningitic doses.

Blood culture taken at admission grew *Candida tropicalis* sensitive to amphotericin B and voriconazole, hence fluconazole was switched to amphotericin B on day 20 of life. As a part of the work-up for fungal infection at other locations, a two-dimensional (2D) echocardiography (ECHO) was done, which revealed a 3.5 cm × 5 cm vegetation on the atrial aspect of the tricuspid leaflet with features of mild persistent pulmonary hypertension (PPHN) as suggested by a pulmonary pressure of 20 mmHg measured using tricuspid regurgitation jet, with no associated congenital heart disease (CHD). As the fever was persistent, a possibility of IE was kept, based on the 2D ECHO report along with other clinical findings which satisfied modified Duke's criteria (both major criteria were satisfied-echocardiogram showing valvular vegetation, positive blood culture for organism along with intravenous antibiotic exposure and fever as minor criteria) for IE.

Valvular surgery for vegetation was deferred as the baby was at high risk. Low-molecular-weight heparin (enoxaparin at a dose of 1.5 mg/kg/dose 12 hourly) was administered by subcutaneous route to prevent embolization. Ultrasound abdomen and indirect ophthalmology examinations were normal. Blood cultures sent simultaneously from the brachial vein of the right and left upper limb revealed growth of *C. tropicalis* along with *Serratia marcescens* sensitive to colistin and tigecycline, the latter were added by day 23 of life. Meropenem and vancomycin were stopped. Screening for syphilis, cytomegalovirus, rubella, toxoplasma, chicken pox, and hepatitis virus infections, done for intrauterine growth restriction (IUGR), was negative.

Thus, the neonate was diagnosed to be suffering from neonatal culture-positive sepsis along with pneumonia, meningitis, neonatal cholestasis, and neonatal IE possibly due to umbilical venous catheterization. Enteral feeds with expressed breast milk were started on day 1 of admission and gradually increased. ECHO repeated on days 7 and 14 of admission revealed no change in the size of the vegetation. The platelet count persisted between 25,000 and 30,000/mm^3 [Table 1] but without any active bleeding.

Table 1: Serial investigations of the newborn during the course of illness

Day of life/investigations	Day 1	Day 5	Day 15	Day 25	Day 30	Day 42	Day 47
Hemoglobin (g/dL)	20.0	18.5	16.5	11.0	10.0	9.26	8.2
TLC (per mm^3)	14.26	11.65	4.44	26.36	16.61	15.13	-
DLC (Neutrophil %, Lymphocyte %)			50, 33	45, 46	35, 44	45, 34	
Platelets (per/mm^3)	54,000	12,000	18,000	30,000	25,000	15,000	12,000
Creatinine (mg/dL)	0.4	-	0.24	0.35	-	0.25	-
Total bilirubin (mg/dL)	-	14.4	7.2	4.9	3.5		
Direct bilirubin (mg/dL)	-	1.2	3.1	2.5	1.8		
AST/ALT/alkaline phosphatase (IU/L)	-	-	33/14/110	45/39/-	-		
Albumin (g/dL)	-	-	2.77	2.87	-		
PT (s)/INR	-	-	19.7/1.55	-	-	22.4/1.9	25.8/1.98
Na/K (mEq/L)	-	-	139.7/5	141.68/4.21	-	139.3/4.94	-
Blood sugar (mg/dL)	-	-	65	68	-	58	-
D-dimer (µg/mL)						7.99	-

TLC: Total leukocyte count, DLC: Differential count, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Na/K: Sodium/potassium, PT: Prothrombin time, INR: International normalized ratio

The baby remained on noninvasive respiratory support by HHHFNC until day 42 of life (for 4 weeks after admission at our center) when he developed sudden-onset severe respiratory distress. Invasive ventilation by synchronized intermittent-positive pressure ventilation mode with peak inspiratory pressure 15, positive end-expiratory pressure 6, rate 40/min, and FiO_2 50% was initiated along with intravenous fluids and dobutamine at 7.5 μg/kg/min and nor-adrenaline at 0.1 μg/kg/min. Investigations at this point revealed further decrease in platelets to 15,000/mm^3, prothrombin time 22.4 s, international normalized ratio 1.9 s, and D-dimer 7.99 μg/ml [Table 1], suggestive of disseminated intravascular coagulation. In view of rapid deterioration, voriconazole was added. Further, ECHO on day 42 of life revealed an increase in the size of vegetation causing tricuspid valve flow obstruction and pulmonary pressures of 56 mmHg suggestive of severe PPHN [Figure 1]. As inhaled nitric oxide was unavailable at our center, intravenous sildenafil at 1.6 mg/kg/day as a continuous infusion along with milrinone at 0.5 μg/kg/min was started. Bosentan at 1 mg/kg/dose 12 hourly was added the next day. In view of worsening respiratory distress, the possibility of thromboembolism was kept, and contrast-enhanced computed tomography thorax with pulmonary angiography was performed. It revealed a thrombus in both pulmonary arteries [Figure 2] along with features of infarct in the posterior segment of the right upper lobe [Figure 3] and hypodense focus along the tricuspid valve likely to be infective vegetation. Thrombolysis could not be initiated as he developed pulmonary hemorrhage. Despite all supportive therapies, the patient continued to deteriorate. He developed hypoglycemia requiring a glucose infusion rate of 14 mg/kg/min, and worsening shock requiring dopamine and adrenaline. Following another episode of severe pulmonary hemorrhage, the newborn went into cardiac arrest and died on day 47 of life.

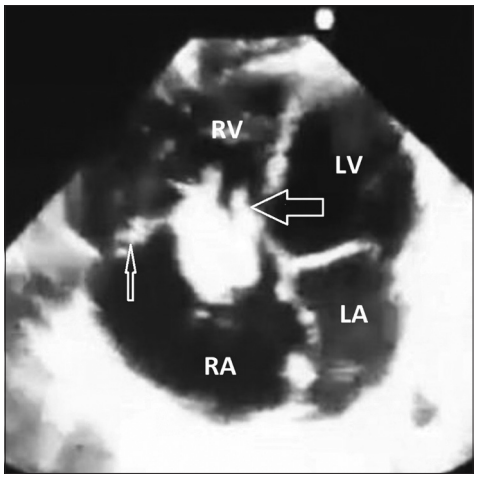

Figure 1: Vegetation (thick arrow) on tricuspid valve (thin arrow) in two-dimensional echocardiography. LA: Left atrium, LV: Left ventricle, RA: Right atrium, RV: Right ventricle

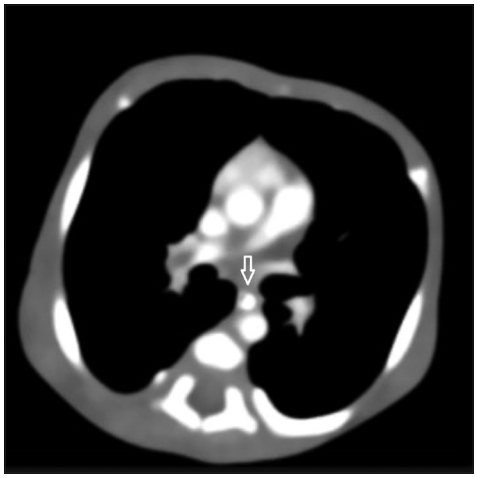

Figure 2: Thrombus in the pulmonary artery (arrow) in contrast enhanced computed tomography of thorax with pulmonary angiography

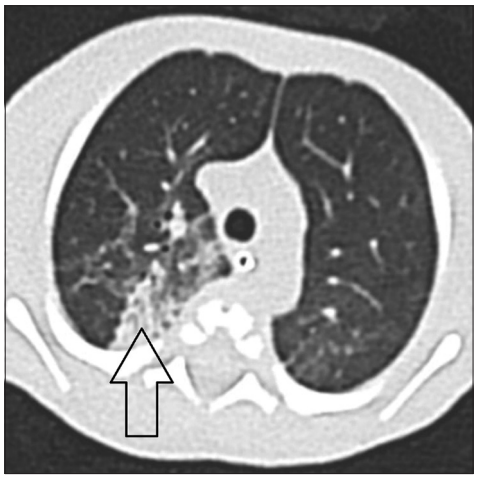

Figure 3: Infarct in the posterior segment of right upper lobe (arrow) in computed tomography thorax with pulmonary angiography

Discussion

The case above describes the fatal course of tricuspid valve IE, in a premature neonate, possibly a complication of umbilical vein catheterization. While neonatal care has improved globally, it has also led to a surge in neonatal sepsis, both due to bacterial and fungal infections, and other complications such as portal vein thrombosis, IE, probably due to advanced invasive procedures.[3,4]

Neonatal IE is rare, 4.3 cases per 100 high-risk investigated patients.[2,5] The analysis of hospital records of 1588 children with IE in Boston, showed that 108 were infants < 1 month of age, comprising 7% of the total.[2] Underlying heart disease has been found in nearly 40% of pediatric IE, majority (80%) being CHD. Among the CHD, cyanotic heart disease, left-sided defects, endocardial cushion defects, and reconstructive cardiac surgery in infants <6 months are more prone to IE.[2] Our case had no underlying heart abnormality. In children without preexisting heart disease, predisposing factors are central venous catheters, immunocompromised children, frequent invasive interventions, institutionalized patients, and premature infants.[6] Our case was premature IUGR, had umbilical

venous catheterization, and prolonged institutionalization on broad-spectrum antibiotics. Duperril *et al*. reported IE in two premature neonates with vegetations present at the tricuspid valve in one and left intra-auricular location in the other.[7] The preterm, very low birth weight, female neonate, reported by Azhar[8] showed moderate pericardial effusion and two masses in the heart, one in the right ventricle and the other in the inferior portion of the posterior mitral valve of the left ventricle.[8]

In pediatric IE, *Staphylococcus aureus* has been found to be the most common organism, followed by *Streptococcus viridans*, other *Streptococci,* and coagulase-negative *Staphylococci*.[2] Not much is known about neonatal IE with organisms implicated being Gram-positive bacteria such as *S. aureus* and coagulase-negative *Staphylococcus* and Gram-negative bacteria such as *Klebsiella pneumoniae, Enterobacter cloacae, Enterococcus faecalis, S. marcescens*, and *Acinetobacter calcoaceticus*.[9] Both preterm neonates reported by Duperril *et al*.[7] harbored methicillin-sensitive *S. aureus*. The term newborn in the report by Avasiloaiei *et al*.[10] had fatal IE due to vegetation on the tricuspid valve caused by *S. marcescens*, which was also seen in our patient. Fungal IE in neonates is even rarer, with high rate of complications.[1,4] Similar to our case, Azhar *et al*.[8] from Saudi Arabia also documented *Candida* in the blood and pericardial fluid cultures in a 32-week preterm neonate.

Long-duration antifungal therapy is advocated in neonatal IE.[4] Surgical intervention in the management of neonatal IE is a dilemma, indicated in the case of severe tricuspid regurgitation, continuing sepsis, or pulmonary embolization of vegetation.[4,5] Fungal endocarditis can lead to thromboembolism, but unusual in the neonatal population, which should be considered in acute respiratory worsening in a case of IE. Urgent treatment with thrombolysis and/or anticoagulants is necessary in such cases.[1,7]

Overall, the mortality rate for premature infants with IE has been found to be significantly higher than that for older infants and children. The large study by Day *et al*.[2] reported that 69.5% of those who died due to IE without preexisting heart disease, were infants, 31.2% of them being premature. Similar to Avasiloaiei *et al*.,[10] our case also had complications of PPHN and succumbed to the illness.

Conclusion

Our case creates awareness regarding the possibility of extreme complications post umbilical vein catheterization in premature neonates, such as IE of the tricuspid valve due to unconventional organisms such as *C. tropicalis* and *S. marcescens*, leading to pulmonary thromboembolism and ultimately death.

Lessons learnt

- Persistent respiratory distress with fever and thrombocytopenia due to fungal sepsis in a premature infant with umbilical lines, may indicate infective endocarditis (IE), underscoring the need for screening by echocardiography
- Infective endocarditis in neonates may be due to unusual organisms like *Candida tropicalis* and *Serratia marcescens*
- Neonatal IE may lead to pulmonary thromboembolism..

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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