Infective Endocarditis Caused by Methicillin-Resistant *Staphylococcus epidermidis* in the Infant of a Mother with Diabetes: A Case Report

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Infective endocarditis (IE) is a rare but severe condition caused by microbial infection of the endocardium. It affects both adults and children with underlying conditions or immunosuppression, including infants of mothers with diabetes (IDMs). We report a case of IE caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE) in a newborn IDM.

A male infant was born at 38 weeks gestation, weighing 5,102 g. His mother had poorly-controlled type 2 diabetes, and the infant had asymmetric septal hypertrophy of the heart. He was admitted to our unit with severe hypoglycemia and respiratory distress necessitating treatment using an indwelling peripherally-inserted central catheter (PICC). The tip of the PICC was moved to the appropriate position because it was initially located in the patient's right ventricle. He was determined to have IE via a positive MRSE blood culture and vegetation in the right atrium. He was treated with vancomycin followed by surgery at 74 days of age to remove the vegetation. He recovered well and was discharged at 92 days of age.

IDMs whose mothers have poorly-controlled diabetes may be at higher risk of IE, particularly if they have hemodynamic abnormalities and indwelling PICCs. However, further studies are warranted to confirm this hypothesis.

Key words: infants of diabetic mothers, infective endocarditis, methicillin-resistant *Staphylococcus epidermidis*, peripheral inserted central catheter

INTRODUCTION

Infective endocarditis (IE) is a severe condition caused by microbial infection of the endocardium [1]. Although it primarily affects adults, children with underlying diseases or immunosuppression are also at higher risk [2, 3]. Common causative agents include *Streptococcus* spp. and *Staphylococcus aureus*. Cases of IE caused by *Staphylococcus epidermidis* are rare, as this pathogen is only known to cause infections in immunocompromised patients or following the use of medical devices [4].

Infants of mothers with diabetes (IDMs) are known to present with various complications at birth, such as hypoglycemia, macrosomia, and cardiovascular abnormalities [5]. These infants may have metabolic and immune abnormalities that increase their susceptibility to infections [6, 7]. However, reports of IE in IDMs remain limited in the literature [8].

Herein, we report a rare case of IE caused by methicillin-resistant *Staphylococcus epidermidis* (MRSE) in an IDM, and discuss potential causes of IE and how it should be managed when vegetation remains following medical treatments in these infants.

CASE

A male infant was born at 38 weeks and 6 days of gestation, weighing 5,102 g (+5.3 SD), by emergency cesarean section because of non-reassuring fetal status, to a mother with poorly-controlled type 2 diabetes. His Apgar scores were 4 and 7 at 1 and 5 min, respectively. His 23-year-old mother had experienced an episode of diabetic ketoacidosis with 13.6% hemoglobin A1c and 457 mg/dL of blood glucose values at 5 weeks of gestation. Although she had received insulin treatment, her compliance during the pregnancy was inconsistent.

The patient was admitted to our neonatal intensive care unit with severe respiratory distress at birth. He was administered continuous positive nasal airway pressure therapy. He exhibited significant hypoglycemia, with a blood glucose level of 4 mg/dL. Although intravenous glucose was administered, his hypoglycemia did not improve. A peripherally-inserted central catheter (PICC) was therefore inserted to deliver high-concentration continuous glucose infusion. Although the patient did not show any symptoms or laboratory findings suggestive of infection, empirical antibiotic therapy with ampicillin and gentamicin was initiated because the causes of his non-reassuring fetal status and respiratory distress remained unknown.

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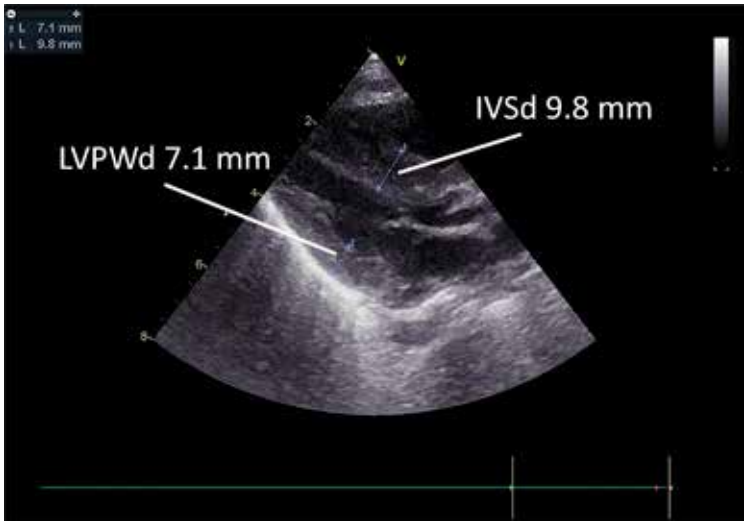

Fig. 1 Long-axis view of the patient's echocardiography on admission. Interventricular septal thickness at end-diastole (IVSd) and left ventricular posterior wall thickness at end-diastole (LVPWd) were 9.8 and 7.1 mm, respectively. Both revealed hypertrophic changes. Asymmetric septal hypertrophy (IVSd/LVPWd = 1.38) was also noted.

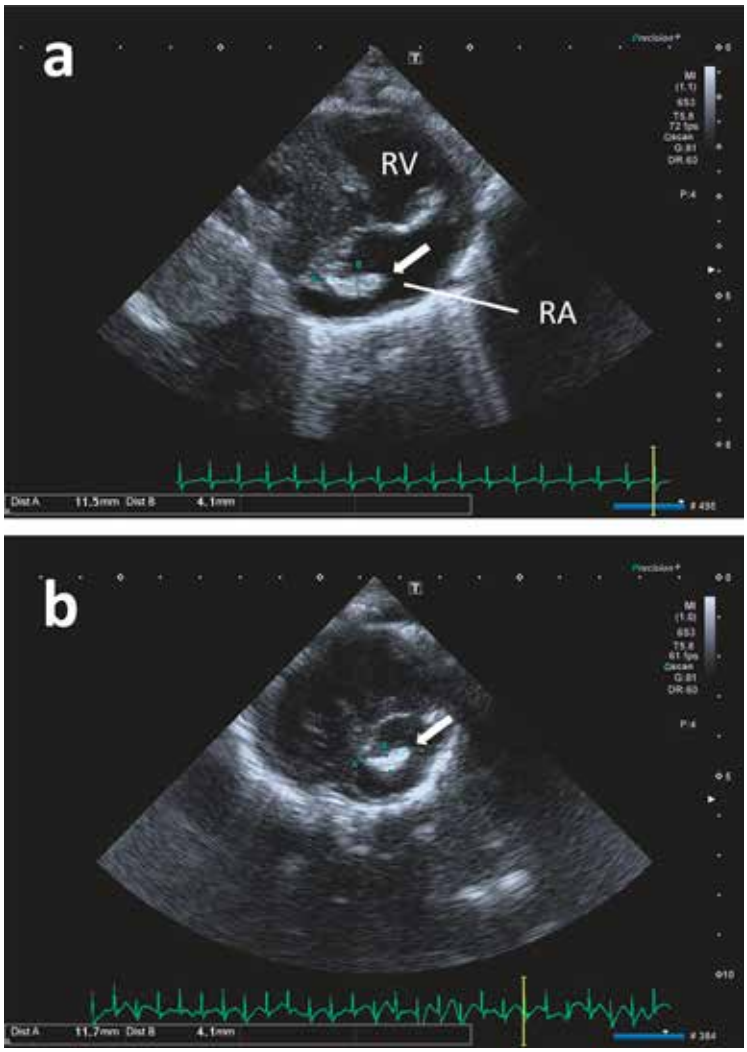

Fig. 2 a) Echocardiography of our infant patient diagnosed with infectious endocarditis at 14 days of age. Vegetation with an associated stalk (white arrow) was observed on the right atrial wall around the posterior leaflet of the tricuspid valve annulus, measuring 11.5 × 4.5 mm. RV, right ventricle; RA, right atrium b) Echocardiography after the completion of antibiotic treatment at 54 days of age. Despite six weeks of treatment with vancomycin, the vegetation (white arrow) showed no significant change in size.

Echocardiography revealed hypertrophic changes of the intraventricular septum in diastole (IVSd) and left ventricular posterior wall in diastole (LVPWd), with thicknesses of 9.8 mm and 7.1 mm, respectively. The patient's IVSd-to-LVPWd ratio of 1.38 indicated asymmetric septal hypertrophy (Fig. 1). Fortunately, outflow in the left ventricle was not restricted, although mild tricuspid regurgitation was observed.

At 1 day of age, the PICC tip was confirmed to be located in the infant's right ventricle of the infant. It was therefore immediately removed and repositioned in the appropriate region. On the same day, the patient's C-reactive protein (CRP) level increased to 2.1 mg/dL without any symptoms of infection. However, his body temperature rose to 37.9°C in the evening. Close observation and continued antibiotic administration were performed to address this.

At 2 days of age, his general condition was stable except for his body temperature, which remained elevated at 37.6°C. Although his white blood cell count was 8,100/μL, his stab cell count was 24%, indicating a leftward shift. His platelet count had decreased to 115,000/μL, and his CRP level was significantly elevated, to 17.38 mg/dL. The PICC was removed to rule out catheter-related bloodstream infection (CRBSI). The ampicillin dose was increased to 200 mg/kg/day, and the 200 mg/kg/day cefotaxime was replaced with gentamicin following sepsis workup testing. Intravenous immunoglobulin was also administered. At 3 days of age, *Staphylococcus* species were isolated from blood cultures in an interim report. Therefore, vancomycin was administered as an alternative to ampicillin. Other cultures, including those of the cerebrospinal fluid and the PICC tip, were sterile. At 7 days of age, MRSE was isolated from the patient's blood culture from day 2. The patient's low-grade fever, of 37.6–37.9°C, occurring 1–2 times per day, was recorded until 9 days of age. Although his CRP values gradually improved until 8 days of age, they began to fluctuate between 0.6–3.10 mg/dL thereafter. Further evaluations were therefore performed to clarify the focus of the infant's suspected infection. The results of repeat blood cultures were sterile. At 14 days of age, echocardiography revealed 11.5 × 4.1 mm of vegetation with a stalk in the right atrial wall, around the posterior leaflet of the tricuspid valve annulus, confirming a diagnosis of IE (Fig. 2a). Vancomycin was administered for 6 weeks. Although fluctuations in the patient's CRP values continued until day 29, they improved thereafter, became negative at 40 days of age, and remained negative once the treatment was completed. Despite vancomycin treatment, the vegetation remained, with an unchanged size (Fig. 2b). The patient was therefore transferred to another hospital for surgical treatment at 69 days of age. The vegetation, which had a stalk attached to the atrial wall between the tricuspid valve annulus, coronary sinus, and inferior vena cava, was completely excised at 74 days of age. Pathological findings revealed calcified myxoid fibrous tissue. The patient's postoperative course was uneventful, and he returned to our neonatal intensive care unit at 82 days of age. Immunological tests for immunoglobulins, C3, C4, CH50, and CD4/CD8 ratio were all within normal ranges. The patient was discharged at 92 days of age.

DISCUSSION

Full-term infants with IE are exceedingly rare (as opposed to pre-term ones) — particularly in cases without congenital heart disease. Our patient, however, was a full-term infant without congenital heart disease who developed IE. The fact that he was an IDM may have affected his development of IE. IDM is associated with several complications — including macrosomia, hypoglycemia, hypocalcemia, respiratory distress syndrome, hyperbilirubinemia, and cardiovascular abnormalities — as well as an increased risk of susceptibility to infections [9]. In our case, cardiac abnormalities, hypertrophic changes in cardiac muscles with asymmetric septal hypertrophy (ASH), and an increased risk of infection may have contributed to the development of IE. Appropriate control of maternal diabetes before and during pregnancy is important for preventing the development of IE in IDMs.

Three major factors may contribute to the development of IE in infants. The first is CRBSI. MRSE was isolated from our patient's blood culture at 2 days of age. The infant required an indwelling PICC to treat severe hypoglycemia. Such devices represent a well-known risk factor for CRBSI. The PICC tip was initially located in the patient's right ventricle. The catheter passed from the right atrium to the right ventricle through the orifice of the tricuspid valve, leading to tricuspid regurgitation that may have worsened during the period of mispositioning. If CRBSI occurs in such conditions, the risk of IE increases. It was unclear whether CRBSI occurred in our patient because a bacterial culture of the catheter's tip was sterile.

The second major factor is hypertrophic changes in IVSd and LVPWd caused by ASH, which represents a frequent complication in IDMs [10]. ASH causes hemodynamic abnormalities that may be related to the development of IE [11].

Third, infants inherently have lower immune function. Diabetes is also well known to impair immune function and increase susceptibility to infection [12–14]. Specifically, maternal hyperglycemia can lead to neutrophil dysfunction and impaired white blood cell function in the fetus, weakening its immunity against infections [15]. Although our patient's immunological tests performed before discharge were normal, abnormal findings may have been detected if similar tests had been performed during the early neonatal period.

The etiologic agents of neonatal IE are most likely to be *Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella pneumoniae, Enterobacter cloacae, Enterobacter faecalis,* and *Streptococcus* species such as *Streptococcus sanguis* [16]. Among these, *Staphylococcus epidermidis* is particularly capable of adhering to catheters and forming biofilms [17]. It also shows particularly high resistance to antibiotics. *Staphylococcus epidermidis* isolates, particularly MRSE variants, have been reported with increasing frequency and may be intractable to treatments in newborns — particularly pre-term ones [18]. MRSE was identified in blood cultures from our case, which was determined to be the cause of IE. Antibiotic treatments ultimately proved to be ineffective for reducing the size of the vegetation that had resulted from this infection. The remaining vegetation might have affected his hemodynamic conditions or caused

the development of embolic events in the future; because of this, we decided on surgical intervention.

Successful treatment of IE using recombinant tissue plasminogen activators (r-TPAs) has been reported in children, including newborns. However, few reports exist in the literature of r-TPAs being used to reduce intracardiac vegetation size in full-term infants. Moreover, severe complications associated with r-TPAs include intracranial, pulmonary, and gastrointestinal hemorrhages caused by emboli [19, 20]. On the other hand, surgical interventions are also associated with a high mortality rate in newborns, particularly pre-term ones. Our infant patient in this case was full-term, and had grown to 6.8 kg at 2 months of age when surgical intervention was considered to remove his remaining intracardiac vegetation. We therefore elected to proceed with the surgical intervention over r-TPA, and successfully removed the vegetation without complications. Whether surgical interventions should be generally preferred to r-TPA, however, remains unclear. At present, decisions regarding optimal treatment approaches should be made on a case-by-case basis.

We present a case of IE caused by MRSE in an IDM. Infants born to mothers with poorly-controlled diabetes may be at higher risk of IE because they often have multiple complications such as hemodynamic abnormalities, and require intensive care such as invasive respiratory support and indwelling PICC placement. Further studies are warranted to clarify the association between IDM, severe complications, and the development of IE.

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CONFLICTS OF INTEREST

The authors declare no conflict of interests associated with this report.

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INFORMED CONSENT

Written informed consent was obtained from the patient's family for publication of this report.

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