Neonatal *Candida albicans* Septic Thrombosis of the Portal Vein followed by Cavernous Transformation of the Vessel

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We report two premature neonates with *Candida albicans* septic thrombosis of the portal vein who developed, in very early childhood, the sonographic appearance of cavernous transformation of the vessel and/or clinical signs of extrahepatic portal hypertension.

**CASE REPORTS**

**Case 1.** A 1,980-g male infant, who was the second infant delivered, was born by emergency cesarean section for fetal distress after a 34-week-triplet gestation to a 35-year-old primigravida mother. Except for premature labor, her pregnancy had been otherwise normal, without prolonged rupture of membranes or maternal fever. The infant had respiratory distress immediately after birth and was therefore admitted to the neonatal intensive care unit (NICU), where he was treated for 2 days with nasal continuous positive airway pressure (CPAP) and for 5 days with oxygen therapy. On admission to the NICU, a polyvinyl chloride 5 French catheter was inserted into the umbilical vein, and intravenous ampicillin and netilmicin were started for suspected sepsis. The catheter tip was noted to be in the inferior vena cava. Blood culture obtained on admission gave negative test results, and antibiotics were discontinued after 3 days. On postnatal day 8, he developed apnea and bradycardia, irritability, feeding difficulties, and abdominal distension. The same day, the catheter was removed, the catheter-tip, blood from peripheral veins, and urine cultures were taken, and the infant was started on teicoplanin therapy. While the infant continued to be symptomatic, on postnatal day 10, the laboratory report for the positive cultures of the catheter tip indicated a pure growth of *Candida albicans* and treatment was changed to oral fluconazole. On postnatal day 11, the blood culture performed 3 days earlier was reported to have yielded a heavy (defined as ≥50 CFU/ml) (24) growth of *C. albicans* (sensitive to fluconazole and amphotericin B). He continued treatment with fluconazole for 6 weeks and on day 11 started a 6-week intravenous amphotericin B treatment. Soon after the positive blood culture result, a disseminated fungal workup including abdominal and cranial ultrasound, echocardiogram, and ophthalmologic evaluation was performed. The echocardiogram, cranial ultrasound, and ophthalmologic evaluation were negative. Abdominal gray-scale ultrasound showed that both right and main portal veins were completely filled with hyperechoic thrombus. The spleen was of normal size, but the liver appeared slightly enlarged without sonographic abnormalities of the hepatic parenchyma or of the biliary structures. A second cranial ultrasound revealed, in the parietal and temporal lobes, multiple, bilaterally round hyperechoic lesions with echogenic rims, which were consistent with intracranial abscesses (18). A peripheral venipuncture blood culture obtained 1 week after initiation of antifungal therapy was still positive for *C. albicans*. However, it became sterile 11 days after antifungal treatment was started. At 35 days of age, the cranial ultrasound became normal, but the abdominal gray-scale ultrasound showed a cavernous transformation of the portal vein (32). The sonographic appearance included (i) failure to visualize the extrahepatic portal vein, (ii) demonstration of high-level echoes in the region of the porta hepatis, and (iii) multiple tortuous collateral vessels in the porta hepatitis (Fig. 1). At 3, 6, 9, 12, and 18 months of age, the infant had sonographic examinations, each of which confirmed the features of cavernous transformation of the portal vein, along with a normal-size spleen and liver. At each of these five follow-up examinations, Doppler spectrum evaluation signaled low-velocity hepatopetal venous flow in the multiple collateral vessels at the level of the porta hepatitis. The child is now 19 months old and has not developed overt features of portal hypertension.

**Case 2.** A 1,560-g male infant was born by emergency cesarean section for fetal distress after a 33-week-singleton gestation to a 32-year-old primigravida mother. Pregnancy was complicated by premature labor and preterm rupture of membranes, without maternal fever. Soon after birth, he was transferred for respiratory distress to the NICU, where he was treated for 5 days with CPAP and for 7 days with oxygen therapy. On admission to the NICU, a polyvinyl chloride 5 French catheter (with its tip positioned in the inferior vena cava) was inserted into the umbilical vein, a blood specimen for a heavy growth of *C. albicans* (sensitive to amphotericin B), for 1 week after initiation of antifungal therapy was still positive for *C. albicans*. For 50 CFU/ml) (24) growth of *C. albicans* (sensitive to fluconazole and amphotericin B). He continued treatment with fluconazole for 6 weeks and on day 11 started a 6-week intravenous amphotericin B treatment. Soon after the positive blood culture result, a disseminated fungal workup including abdominal and cranial ultrasound, echocardiogram, and ophthalmologic evaluation was performed. The echocardiogram, cranial ultrasound, and ophthalmologic evaluation were negative. Abdominal gray-scale ultrasound showed that both right and main portal veins were completely filled with hyperechoic thrombus. The spleen was of normal size, but the liver appeared slightly enlarged without sonographic abnormalities of the hepatic parenchyma or of the biliary structures. A second cranial ultrasound revealed, in the parietal and temporal lobes, multiple, bilaterally round hyperechoic lesions with echogenic rims, which were consistent with intracranial abscesses (18). A peripheral venipuncture blood culture obtained 1 week after initiation of antifungal therapy was still positive for *C. albicans*. However, it became sterile 11 days after antifungal treatment was started. At 35 days of age, the cranial ultrasound became normal, but the abdominal gray-scale ultrasound showed a cavernous transformation of the portal vein (32). The sonographic appearance included (i) failure to visualize the extrahepatic portal vein, (ii) demonstration of high-level echoes in the region of the porta hepatis, and (iii) multiple tortuous collateral vessels in the porta hepatitis (Fig. 1). At 3, 6, 9, 12, and 18 months of age, the infant had sonographic examinations, each of which confirmed the features of cavernous transformation of the portal vein, along with a normal-size spleen and liver. At each of these five follow-up examinations, Doppler spectrum evaluation signaled low-velocity hepatopetal venous flow in the multiple collateral vessels at the level of the porta hepatitis. The child is now 19 months old and has not developed overt features of portal hypertension.
amphotericin B. Cranial ultrasound, echocardiogram, and ophthalmologic evaluation were negative. Abdominal gray-scale ultrasound showed that the main portal vein was completely filled with hyperechoic thrombus. The spleen was normal size, but the liver appeared slightly enlarged, without sonographic abnormalities of the hepatic parenchyma or of the biliary structures. A peripheral venipuncture blood culture obtained 5 days after initiation of antifungal therapy was still positive for C. albicans. However, it became sterile 9 days after antifungal treatment was started. At one month and a half of age, the abdominal gray-scale ultrasound showed a cavernous transformation of the portal vein. The sonographic appearance included an abnormal echogenic cord replacing the portal vein, along with a few tiny collateral vessels in the porta hepatis. At 12 months of age, on physical examination splenomegaly was the presenting feature of extrahepatic portal hypertension (EHPH). At 24 months of age, esophageal varices were seen on endoscopic examination and injection sclerotherapy was performed. He is now 39 months old and has not experienced bleeding from the esophageal varices (or any other source).

In adults, the primary cause of portal hypertension is some form of acquired cirrhosis, whereas a common etiology in childhood is extrahepatic portal vein obstruction (EPVO), usually due to portal vein thrombosis (PVT) (21). Because PVT seldom causes clinical problems during the neonatal period, the majority of cases remain unrecognized and are fortuitously found later. The natural history of EHPH can be relatively unpredictable. Bleeding from esophageal varices is the most common presentation. However, the time from portal vein obstruction to hemorrhage appears to be quite variable, though more than half of the patients in many series with EHPH do not experience bleeding until after age 6 years (28). Splenomegaly is the next most common presenting feature in portal vein obstruction, and asymptomatic splenomegaly in a child without hepatocellular disease may be discovered on routine physical examination (28). An important feature of EPVO is cavernous transformation of the portal vein. Current thinking holds that it represents recanalization of the portal vein with development of periportal collateral channels in cases of chronic portal vein obstruction (32). As shown by Fonkalsrud (11), approximately 25% of patients with PVT develop spontaneous venous collaterals sufficient to permit long-term nonoperative management. The sonographic appearance of the cavernous transformation has been well described but has not yet been documented, to our knowledge, in very early childhood (16, 32). Overall, these factors make it extremely difficult to be certain of the etiology.

Known factors associated with the initiation and propagation of thrombosis, in general, include endothelial damage during catheter placement, composition of the infusate, catheter characteristics, and the duration and location of catheter placement (16). Patient variables that in neonates can increase the predisposition to thrombus formation include low birth weight, birth hypoxia, and sepsis. In our two cases, several risk factors were identified that correlated with catheter-related thrombosis, any one of which or a combination of which could have contributed to the development of EPVO. Among them, the following were identified: (i) prematurity, (ii) a catheter being present for 1 week or more, (iii) size and type of catheter, and (iv) systemic infection. The true contribution of each factor to EPVO is still unclear, but most of the studies are retrospective. In a review of 13 major retrospective studies (1, 6, 9, 12–14, 17, 19, 20, 22, 23, 26, 29), a positive history of neonatal infection was available in a percentage varying from 3.5 to 56.2%, in most of them, the origin being the umbilicus. In only six of these studies (9, 13, 19, 23, 26, 29) was a positive history of cannulation of umbilical vein available, with a percentage varying from 4.2 to 38.4%. Some characteristics of these studies have limited their generalizability. These include (i) identification of the patients with the target condition through chart review of data recorded 1 to 3 decades prior to the retrospective survey and (ii) analysis of patients with a wide age range as evidence of long-standing clinical disease. On the other hand, there are two major prospective studies which were designed to establish, by means of ultrasonography, the incidence and natural history of PVT related to an umbilicus venous catheter (16, 34). Yadav et al. concluded that umbilical vein catheterization and sepsis do not lead to development of PVT (34), while Kim et al. concluded that spontaneous resolution is expected in many cases of PVT (16). Major limitations of these studies include the relatively small numbers of patients, exclusion of patients with hypertonic solutions through the umbilical venous catheter, catheter duration restricted to minimal time, or a short follow-up. The appropriate question with these studies is how closely the targeted study population resembles the patient population. To complicate matters further, in both retrospective and prospective studies, there has been no definition of culture-proven neonatal sepsis string enough to distinguish culture contaminants from true culture-proven sepsicemias (8). As a result, it must be emphasized that all these studies failed to mention the microbial...
etiology of neonatal sepsis. Also absent from such publications are unequivocal criteria to exclude sepsis in neonates with culture-negative results. In fact, culture can be falsely sterile because of the low yield caused by insufficient sample volumes, intermittent or low-density bacteremia, or suppression of bacterial growth by earlier (i.e., intrapartum) antibiotic administration. Theoretically, this would lead to an underrepresentation of truly infected newborn infants (8).

Against this background, our two present cases had microbiologic evidence of systemic disease due to C. albicans, and both fulfilled the following criteria for intravenous catheter-related septic thrombosis: (i) high-grade candidemia, (ii) a vascular catheter in place prior to the onset of candidemia, (iii) no plausible extravascular source, (iv) persistence of candidemia, and (v) clear-cut evidence of obstruction of the involved vein (27). Although catheter-related candidemia and catheter-related thrombosis are relatively frequent findings, Candida septic thrombosis of the deep vascular structures is a rare but probably underdiagnosed disorder. Before 1978 it was almost always an autopsy finding (3, 25). Jarett et al. published a report on the first successfully treated patient in 1978 (15); since then, a few cases have been reported in adults (4) as well as a few in children (5). The disorder has rarely been reported in the newborn infant (2).

The increasing incidence of candidemia and nosocomial candidal infections over the past decades and the high incidence of catheter-related thrombosis (7) suggest a higher frequency of Candida septic thrombosis of the vascular structures than is reported in the literature. Risk factors for the development of major candidal infections are well known, and risk factors for the development of Candida infection of the vasculature are largely the same as those reported for candidal infections (33). Both peripheral and deep vascular structures have been involved as well as both the venous and the arterial sides of the circulation and implanted prosthetic vascular materials (10). A case of PVT due to C. albicans has been reported in an adult patient with alcoholic hepatic cirrhosis (30). There are, however, to our knowledge, no reported cases in children and newborns of C. albicans septic thrombosis of the portal vein. The pathogenesis of catheter-associated fungemia is not well understood. Candida that arises from the alimentary tract and portal venous circulation (31) may enter the systemic circulation, leading to secondary infection of the vascular catheter. In this situation, the catheter in our two cases might have been the target rather than the source of fungemia, but it might have continued to serve as the source of sustained candidemia as organisms proliferate on the catheter surface. Vascular catheters might, however, have also served as a primary source of fungemia (31). Either primary or secondary infection is a valid hypothesis about which our data permit no more than speculation.

When Candida disseminates, multiple organs are usually involved, with the kidney, brain, myocardium, and eye the most common. As most cases of thrombosis of deep vascular structures are detected by ultrasonography, a further, large assessment of the sonographic appearances of the portal vein in neonates and infants with sustained candidemia and their relationship to clinical and therapeutic outcome seems warranted.

REFERENCES
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bosis with particular reference to the role of infection and exchange trans-


