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Case report

Hepatic abscess due to *Candida* species in neonates: Case reports in Vietnam

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ABSTRACT

Neonatal hepatic abscess (NHA) is a fatal condition in neonates. NHA can be caused by many organisms including bacteria, parasites, and fungi. Fungal NHA is a rare but troublesome cause in terms of diagnosis and treatment. We present three cases of fungal NHA caused by Candida. In these three cases, different underlying problems associated with NHA had been found.

Introduction

Neonatal hepatic abscess (NHA) is a rare and devastating condition. We present three cases of NHA following a *Candida infection in* a children's hospital in Vietnam.

Gram-positive cocci and gram-negative bacilli are common causative pathogens of NHA [1–4]. In rare cases, fungi have been reported to cause liver abscesses [5]. NHA has undetermined or identifiable etiology such as catheter-related bloodstream infections, particularly the umbilical vein catheterization. The other secondary septic conditions are the result of ascending infection via the portal circulation, or hematogenouse dissemination through the biliary tract or direct spread from surrounding structures [1]. Symptoms of NHA are often nonspecific and may be misdiagnosed with ongoing sepsis. Regardless of the cause, the diagnosis is based primarily on radiological findings.

Case reports of diagnosed hepatic abscess caused by *Candida* infection

Case 1: An 11-day-old male, preterm 31 weeks neonate, born by Cesarean section due to bleeding placenta previa with birth weight 1400 g, corresponding to his age

The infant cried at birth and presented with respiratory distress syndrome. He was supported with conventional ventilation, surfactant replacement therapy, introduction of umbilical venous catheter (UVC) in a provincial hospital. The infant's condition worsened and required being transferred to the National Children's Hospital.

On admission, the patient experienced respiratory failure. Supported with CPAP, FiO2 40%, SpO_2 96%, his heart rate was 160 bpm with poor perfusion, pale skin, and abdominal distension. The liver was 3 cm below costal margin with no splenomegaly. Dark gastric fluid and jaundice were present as well. The UVC had been inserted for eleven days. Results of laboratory tests were as follows: white blood cells (WBC) 11.2 G/L, Neutrophil 60%, Hemoglobin (Hb) 9.9 g/dL, platelet 63 G/L, and C-reactive Protein (CRP) 68.8 mg/L. Liver enzymes and kidney function were within normal range. He presented with no coagulation disorders. Abdominal X-ray was significant for incorrect positioning of the umbilical catheter and an air bubble in the right upper quadrant (Fig. 1). Cardiac sonography found a large ductus arteriosus. There is no abnormality in cardiac laboratory tests.

The initial diagnosis was necrotizing enterocolitis with sepsis and patent ductus arteriosus. The umbilical catheter was immediately withdrawn. The patient received respiratory support, broad-spectrum antibiotics, and supportive treatment. After three days of treatment, the patient demonstrated spontaneous breathing with no oxygen supplementation.

For better clarification of the diagnosis, blood cultures on the day of admission yielded *Candida pelliculosa*; thus, Amphotericin B lipid complex (Ampholip) was administered. The abdominal ultrasound showed a cystic liver mass 30×33×40mm with air and fluid inside the mass. Computerized tomography (CT) scan revealed a liver abscess with air and fluid inside a thickened wall (Fig. 2). The abscess, positive for *Candida,* was drained under ultrasound guidance. On Doppler ultrasound, no portal vein or hepatic vein thrombosis were present. The patient then received Caspofungin. After five weeks of treatment, the patient was showing weight gain and demonstrated good feeding habits. No mass was found on the liver and his repeated blood culture was

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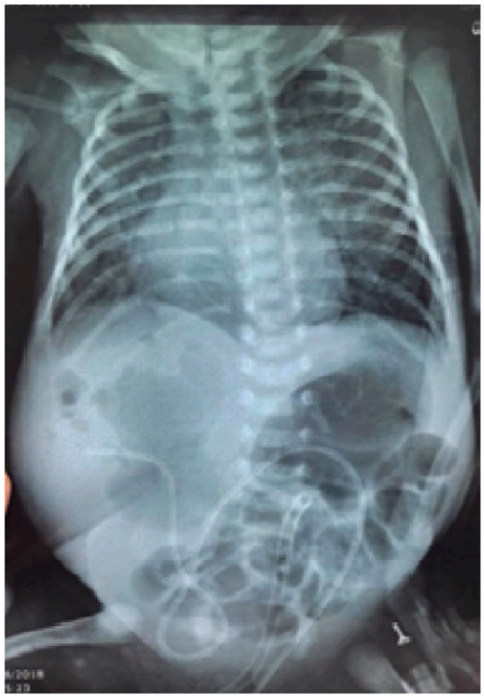

Fig. 1. Wrong position of umbilical catheter on abdominal X-ray in Case 1.

negative. The infant was discharged.

Case 2: A 15-day-old male, preterm 27 weeks neonate, birth weight 900 g (suitable for the gestational age), vaginal delivery

The infant presented with respiratory distress syndrome after birth and was treated with surfactant replacement therapy and ventilation in a local hospital. Even though the respiratory failure was resolved, at the age of fifteen days, the infant's condition deteriorated. Presenting with abdominal distention and increased inflammation markers, the infant was transferred to the National Children's Hospital.

On admission, he was supported with oxygen via nasal prongs. Breath rate was 55 bpm; SpO_2 was 90% with no respiratory retraction. Circulation dysfunction was evident: heart rate of 140 bpm, systolic murmur, weak pulse, pallor, and poor perfusion. Abdominal distension was evident. Physical examination revealed that the patient's liver was 3 cm below costal margin with no splenomegaly. Results of laboratory tests were as follows: WBC 13.8 G/L, Neutrophil 54%, Hb 9.5 g/dL, platelet 5 G/L, CRP 69 mg/L, decreased IgG, IgM, IgA levels, increased liver enzymes and bilirubin level. A coagulation disorder with prothrombin 18%, activated partial thromboplastin clotting time (aPTT) 73 s, and fibrinogen 0.68 g/L was also present. Abdominal ultrasound revealed air in the portal vein, suspected portal vein thrombosis, and free intra-abdominal fluid. Abdominal CT scan showed thrombosis causing total obstruction of portal vein and left and middle hepatic veins. Cardiac ultrasound detected a large ductus arteriosus and blood tests for heart disease are within normal limits.

The patient was intubated and ventilated, treated with broad

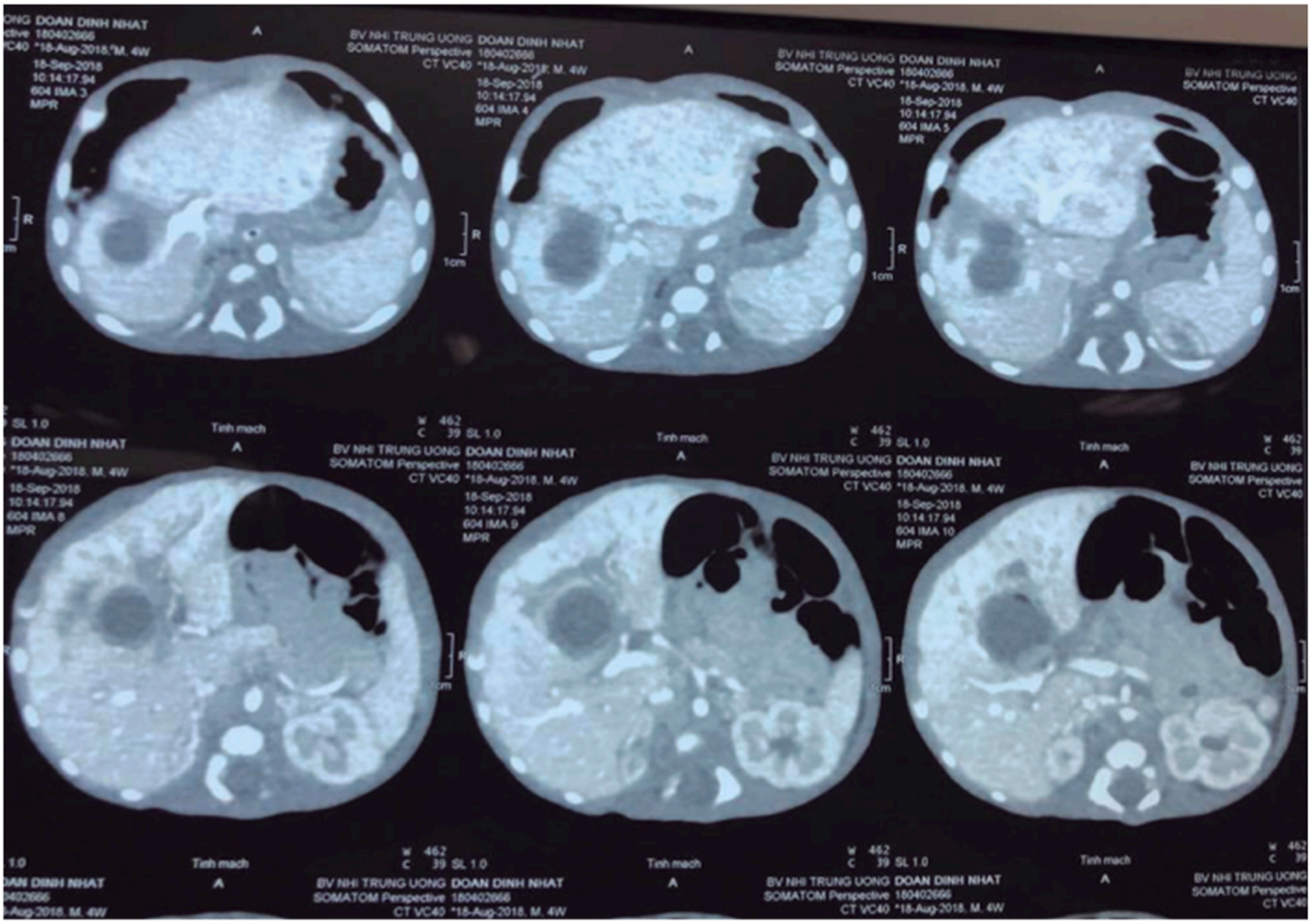

Fig. 2. Liver abscess on abdominal CT scan in Case 1.

spectrum antibiotics, antifungal prophylaxis, and total parenteral nutrition. He was transfused with fresh frozen plasma and platelets as well as administered low molecular weight heparin (Lovenox). On the third day of admission, the patient's blood and urine cultures were significant for *Candida tropicalis*. Despite intensive treatment, his clinical status worsened. The patient died on the fourth day following admission.

Case 3: A term male infant, spontaneous vaginal delivery at 38 weeks, with the birth weight of 3300 g (appropriate for gestational age)

The infant cried at birth without asphyxia. Three hours after birth, the infant developed respiratory distress and was transferred to the referring hospital's NICU. He was intubated immediately and received emergency resuscitation. UVC was placed on admission. Chest X-ray indicated proper positioning of UVC (Fig. 3).

Total parenteral nutrition was initiated on day one of life. Vital signs were unstable indicating circulation dysfunction. Two inotropes were administered. Initial laboratory tests indicated early onset infection with raised C-reactive Protein (CRP: 14.5 mg/L) and leukocytosis (WBC count: 39 G/l).

Because his status was unstable, he was transferred to our NICU at the National Children's Hospital on the second day of life. He was initially diagnosed with early onset infection. As a result, three antibiotics–Ampicillin, Cefotaxime, and Tobramycin–were administered. The umbilical vein catheter administering TPN and inotropes remained in position until the fifth day of life. All sample cultures taken on admission to our NICU were negative. Within the first four days of life, markers of inflammation gradually decreased. He began feeding on day four and was extubated on the fifth day of life.

On day six of life, the patient's condition showed clinical deterioration: abdominal distension, lethargy, and hepatomegaly palpable 3 cm below the costal margin. No splenomegaly and no other abnormal systemic findings were found. Laboratory tests illustrated leukocytosis and increased CRP level (133 mg/L). Cardiac function tests are normal. Abdominal X-ray showed an enlarged liver with a small 10 × 15 mm air bubble in the right side of the liver (Fig. 4). Abdominal ultrasound demonstrated a large mass measuring 74 × 77 mm located in the right hepatic lobe mainly, suggestive of liver abscess.

To further clarify the patient's condition, abdominal CT performed

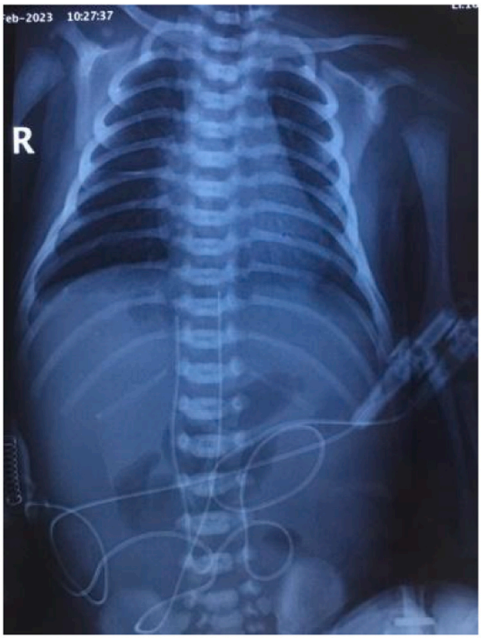

Fig. 3. Position of umbilical vein catheter on X-ray in Case 3.

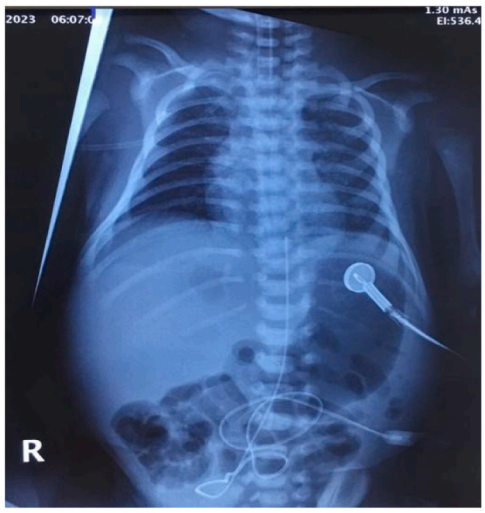

Fig. 4. Liver abscess after umbilical vein catheter withdrawn on X-ray in Case 3.

immediately showed a large heterogeneous, hypodense lesion of 45×55×68 mm located in both the right and left lobes of the liver. The lesion contained fat and gas. Post-contrast, rim enhancement with hepatic perfusion disorder of surrounding hepatic parenchymal was evident. Percutaneous abscess drainage under ultrasound guidance performed on day seven of life resulted in the placement of an indwelling drain. Both cultures of blood and pus from the abscess carried out simultaneously revealed *Candida albicans* with Fluconazole and Amphotericin B sensitivities. Cerebrospinal fluid cultures were sterile. Antifungal therapy–Fluconazole and Ampholip–was administered for ten weeks. Patient's clinical condition progressively improved. However, during treatment in our NICU, the patient needed another percutaneous drainage under ultrasound guidance about one month after the first one.

Control hepatic ultrasound examinations revealed significant regression and calcification of the previous lesion. Infant was discharged to home in healthy condition on the twelfth week of life.

Discussion

Candida infections are one of the leading agents of the late onset sepsis [6] with severe sequelaes and significant morbidity and mortality rate in neonates [7]. The newborns with prematurity, extremely low birth weight, prolonged total parental nutrition administration and broad-spectrum antibiotic therapy have high risks of suffering from the fungal infection [7]. Central venous catheters, especially malpositioning of the umbilical venous catheter, are significant risk factors as well [8].

Neonatal hepatic abscesses are particularly rare in neonates. Previous studies have indicated that there are three cases related to NHA in 11,403 hospitalized newborns [2]. The most popular pathogens are gram positive cocci (*Staphylococcus aureus*) and gram negative bacilli (*Klebsiella* and *Enterobacter*) [1,9]. Moreover, *Candidas spp* is a rare causative agent of neonatal liver abscess, mostly presenting in case reports [3,10]. The main causes resulting in this infection are central line-associated bloodstream infection developing after umbilical vein catheterization or from candidemia following an infection of another part of the body [9]. In our first case, there was a history of malposition of umbilical catheter, and the blood culture was positive for *Candida*. In the second case, the history of misplaced umbilical catheter is unknown, but there is evidence of Candidemia and *Candida* infection of the kidney. In addition, the third case illustrated that the blood culture of the patient without a history of malposition of the umbilical catheter was positive for *Candida*. These findings highlight the common factors resulting in

NHA as a result of *Candida*.

Early diagnosis of NHA is pivotal due to the high rate of morbidity and mortality. Diagnosis of hepatic abscess requires a high index of suspicion based on clinical awareness of ongoing sepsis of unknown origin and a patient who is not responding to routine treatment (especially in neonates with risk factors such as immunodeficiency, umbilical line in situ, long term exposure to antibiotics, and etc) [7]. For infants suspected of having hepatic abscess, a thorough clinical examination and investigations are critical to finding any abnormal manifestations that suggest liver abscess, e.g., abdominal distension and hepatomegaly.

Since clinical manifestations of liver abscess are non-specific and similar to sepsis, abdominal radiography is necessary to confirm a diagnosis of liver abscess. In neonates with liver abscess, findings from the abdominal X-ray may include hepatomegaly and air bubbles in the abscess cavity [11]. Ultrasonography plays an important role in diagnosing liver abscesses since it is noninvasive and can produce a reliable result with a sensitivity ranging from 66% to 90% [12]. Abdominal ultrasound illustrates hepatic abscesses as areas of increased echogenicity and breakdown. In recent years, CT scan is more widely used in diagnosing liver abscess due to a sensitivity of 97% and a diagnostic accuracy of more than 95% in adults [13]. On the other hand, in neonates, the use of ultrasound for diagnosing liver abscess is far more widespread due to its access, availability, and low cost. Serial ultrasound of the liver can be used to monitor the response to treatment. Diagnostic tap for abscess drainage and pathogen identification should be done under ultrasound guidance [14].

A ruptured hepatic abscess can develop serious complications related to neighboring structures, including peritonitis and empyema if there is a rupture in the pleural cavity [9]. Portal vein and hepatic vein thrombosis are unusual complications of liver abscess with an incidence of 24% and 22%, respectively according to a study based on an adult population [15]. In neonates, portal vein thrombosis is a uncommon complication with sporadic cases [16,17]. In our first case, we treated the patient with the combination of antifungal and antithrombotic therapy when he developed portal vein thrombosis. In our second case, the thrombosis obstructed the portal vein, as well as the middle and left hepatic veins, causing the patient's condition to deteriorate quickly.

In general, management of NHA includes early diagnosis and appropriate treatment strategy. Intravenous antibiotic therapy for 4–6 weeks plays an important role [4]. In addition, percutaneous aspiration or surgical drainage can be required to get rid of the pus in particular cases. With hepatic abscess caused by fungi, treatment requires appropriate antifungal therapy. In the past, Amphotericin B and Fluconazole used to be the only antifungal medication for neonatal Candidasis. In recent years, due to the resistance against fluconazole, the use of Echinocandins has increased with some limitations due to side effects [18]. We were successful in antifungal therapy, Amphotericin B and then Echinocandins, with the first and third cases and failed for the second case, perhaps due to late diagnosis and treatment of fungal hepatic abscess.

Conclusion

Neonatal fungal hepatic abscess is rare with detrimental consequences if left undiagnosed and untreated. Therefore, prompt diagnosis and appropriate treatment are necessary to enhance positive outcomes. The diagnosis of fungal liver abscess should be strongly considered if the patients present with sepsis-like symptoms and exposure to risk factors of Candidemia. Ultrasound remains an effective bedside diagnostic tool for diagnosis and management of liver abscess. Appropriate antifungal therapy should be started as soon as possible and continued for at least 4 weeks.

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Ethical approval

N/A.

Consent

The patient provided verbal and written consent for publication.

CRediT authorship contribution statement

Thi Quynh Nga Nguyen: Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Thi Van Nguyen**: Data curation, Writing – original draft. **Thao Nguyen Pham**: Investigation, Writing – review & editing. **Thi Kieu Oanh Ha**: Software, Resources.

Author contributions

TQNN developed the study concept and contributed with TNP and TKOH to collect the data. TQNN and TNP analyzed the data and drafted and edited the manuscript with TVN. All authors have read and approved the final manuscript.

Declaration of Competing Interest

No conflicts of interest to disclose.

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The authors have no conflicts of interest to disclose.

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