FUNGAL ENDOCARDITIS IN A FOUR–MONTH-OLD INFANT – A CASE REPORT

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S u m m a r y. Fungal endocarditis (FE) is an infrequent but serious disease. FE does not usually occur in the structurally normal heart. We present a case of a four-month-old male infant, born prematurely with congenital malformation as evisceration, but without any heart disease. He was hospitalized for the two first months of his life and after 3 weeks of staying at home he was readmitted to the hospital with suspected septicaemia. Fungal endocarditis was the final diagnosis. The child died despite of applying antifungal and antibacterial treatment.
K e y w o r d s: infant, invasive candidiasis, fungal endocarditis, *Candida albicans*

INTRODUCTION

Over a couple of recent years there has been an increase in fungal infections. The frequency of their incidence is estimated for approx. 9-10% out of all nosocomial infections. Systemic mycosis belongs to life-threatening diseases, they are observed very rarely in infants and children. The reported incidence of candida infection in neonatal intensive care units is about 1% but occurs in 4-15% of extremely low birth weight infants [15]. Most frequently, the disease develops slowly, and it is difficult to diagnose and treat.

Fungal infections risks factors include: preceding fungal colonization (of skin, oral cavity, gastrointestinal tract), the long-lasting antibiotic therapy (the number of antibiotics > 4), the central venous line, parenteral nutrition, stomatological and operative procedures, assisted breathing, stay in an intensive care unit, chemiotherapy, and neutropenia. Fungal infection can affect various organs, rarely located in the endocardium.

Infective endocarditis, including its fungal etiology, is mainly observed in children with congenital heart disease [9, 11]. It is caused mainly by bacteria (*Staphylococcus aureus, Streptococcus viridians, Staphylococcus epidermidis, Streptococcus pneumonia, Pseudomonas aeruginosa, Hemophilus influenzae, Escherichia coli, Klebsiella*) followed by fungi (*Candida* sp., *Aspergillus* sp., *Malassezia*) [18]. The commonest causative agent of fungal endocarditis (FE) is Candida albicans, responsible for 24-46% of all FE [6, 10 , 13, 17].

Endocarditis is most frequently bloodstream infection. Initially there are aseptic verrucous lesions which are formed in endocardial stroma. Then endothelial detachment occurs and platelet-fibrinous vegetations are formed. Bacteria or fungi circulating in blood can colonize these vegetations. Consequently, these fragile infectious thrombus formed on valves can detach and cause vascular congestions in different organs.

Fungal endocarditis common symptoms include: fever, chills, loss of appetite, unexplained weight loss, chest pain, muscle and joint pain, night sweats, shortness of breath, persistent cough, heart murmurs. Central nervous system (CNS) symptoms from can also be observed (headache, convulsions, cerebrovascular accidents). Moreover, the following symptoms can occur: tachycardia, arrhythmia, spleen enlargement, joint inflammation, circulatory insufficiency and metastatic infectious foci (meningitidis, pericarditis, abscesses in different

organs) as well as septic pulmonary embolisms and CNS or ocular congestions. Less common endocarditis symptoms include: the appearance of a spotty red rash on the skin, narrow, reddish-brown lines of blood that run underneath the nails, painful raised lumps that develop on the fingers and nails, painful red spots that develop on the palms of hands.

The incidence of infective endocarditis (IE) in children is 0.8-3.3 per 1000 patients [5, 13]. The case frequency of FE is about 1.5-4.0 per 10 million children and it constitutes up to 12% of all pediatric cases of IE [5, 13]. Among children, 63% of cases are described in neonates and infants [13].

The aim of this article is to draw attention to the fact that fungal endocarditis can affect children without any heart diseases and it can be a complication after the long-lasting antibiotic therapy, despite of the antifungal treatment.

CASE REPORT

A 4–month-old male infant, grav.1, part.1, gestational age 37, birth weight 2300g, delivery by the Caesarean section because of intrauterine hypoxia. Apgar scale: 1'- 2 points, 5'- 7 points. The boy was born with congenital malformation as evisceration. Reanimation was done immediately after birth because of severe intrapartum hypoxaemia and respiratory disturbances. Then the boy was transferred to the Intensive Unit Care in Children Hospital in Lublin, and then to the Department of Pediatric Surgery. In the first day of life the operation of draining the intestines to the abdominal cavity was performed with the resection of the right necrotic testis localized among the loops of intestines. Intestinal motility disturbances as well as pneumonia and peritonitis were observed after the operation. Because of these complications, the boy remained intubated for the first month of his life and his health condition was bad. From the first day of his life the antibacterial and antifungal therapy was applied (ampicillin, gentamycin, fluconazole). Bacteriological cultures were positive: in blood culture – the presence of *Candida albicans*, in pharyngeal and nasal swabs – the presence of coagulase-positive staphylococcus. After 3 weeks of hospitalization the child's condition was still severe, only minor progress in recovery was observed. Respiratory failure, pneumonia with atelectasis and high fever persisted as well as intestinal motility disturbances which demanded intravenous nutrition. Some elevated inflammatory markers were noticed in laboratory investigations (CRP – 10,0 mg/dl, WBC – 36000/ul, n-76%, l-16%, m-8%, ESR – undetectable). Moreover, leucocyturia and the high level of antibodies against human cytomegalovirus were detected. Chest X-ray showed cardiomegaly as well as pneumonia, and at the same time voiding cystourethrogram showed the right vesicouretic reflux. Echocardiography and electrocardiography, repeated several times, showed no abnormalities. In the next blood culture Candida albicans as well as coagulase-positive staphylococcus were still present. The antifungal and antibacterial therapy was applied in accordance with bacteria and fungus antibiotic-sensitivity (Meropenem, Vancocin, Cefoperazone, Fluconazole, Amfothericin B) as well as Ganciclovir. After 8 weeks of intensive treatment - blood culture tests, repeated four times, were negative and inflammatory markers levels were normal. Echocardiography and electrocardiography, performed again, showed no abnormalities. After 82 days of the hospital stay, the boy was discharged from hospital in good condition. At discharge the child was asymptomatic, but after the next three weeks he was readmitted to the Department of Newborn and Infants Pathology with suspected septicemia. The significant deficiency of body mass (< 10 percentile), pneumonia, splenomegaly, bloated abdomen (disturbances of intestine motility) were found on physical examination. The body temperature was normal during the first days of hospitalization, then septic fever was observed. The child's condition was constantly worsening, the symptoms of respiratory and circulatory insufficiency appeared. The high levels of serum inflammatory markers were noticed in laboratory tests. The result of cerebrospinal fluid examination was normal. Chest X-ray showed cardiomegaly, yet pulmonary thromboembolism was negated in CT of lungs. Blood culture was positive and showed the presence of *Candida albicans* with antibiotic-sensitivity to Amphothericin B and Ketoconazole.

Echocardiography was performed again due to cardiomegaly, tachycardia and systolic murmur appearance (Fig. 1). Its result showed: an echo on tricuspid valve which could reflect fungal or bacterial outgrowth balloting between the right atrium and ventricle; tricuspid insufficiency; an additional echo inside the right ventricle connected with papillary muscles and moving synchronously with the heart beat on the inflow route to the right ventricle; enlarged right ventricule with myocardium hypertrophy; enlarged right atrium and pulmonary artery; small left ventricule (16 mm

in transverse cross-section – being the lower limit of normal result).

Finally, sepsis and candida endocarditis were diagnosed. The very intensive anti-inflammatory therapy was applied (antifungal and antibacterial therapy as well as systemic GKS and intravenous immunoglobulines). Nevertheless, the boy's condition was constantly worsening and the patient died as the consequence of circulatory insufficiency.

DISCUSSION

There is no doubt that neonatal *candidemia* carries a significant risk of morbidity and mortality [8, 23, 24]. This risk is mostly related to delayed diagnosis. The risk increases when the infection occurs in highly susceptible individuals, such as premature, immunocompromised or seriously ill infants requiring the prolonged use of broad spectrum antibiotics [2]. Candida is present as the part of the normal intestinal flora. Because of superinfection (usually resulting from chemotherapy, the antibiotic therapy and hematologic abnormalities such as thrombocytopenia), hematogenous dissemination may follow. Among patients with invasive candidiasis, the most common organ involved is the kidneys with the brain being the second most common organ involved [19]. Candida infections may also result in abscess formation. The invasion of the blood vessel walls by the fungus is a possible cause of the disease. The source of fungi is believed to be septic emboli. Rarely, these emboli invade the vascular wall instead of producing vascular occlusion [14, 21].

The most consistent risk factor for acquiring candidemia is the use of broad spectrum antibiotics. It is believed that antibiotics suppress normal bacterial flora which in turn permits unopposed Candida proliferation [2]. Candidemia may be associated with invasive candidiasis, defined as infection of at least one normally sterile extravascular site such as the eye, central nervous system, heart, lung, kidney, liver, or spleen [7]. Risk factors for invasive candidiasis in children with candidemia are poorly defined. Premature infants (gestational age < 32 weeks) and immunocompromised children are at higher risk of invasion [7]. Upon candidemia identification, the evaluation of organ invasion evidence should be made, including: echocardiograms, dilated ophthalmologic examinations, chest CT scans and abdominal ultrasounds [7]. In our patient, all above mentioned imaging studies were repeated several times.

The fungal endocarditis occurrence is on the rise, reported in the last decade in infants and children secondary the central venous line use, the prolonged broad spectrum antibiotics use and neonatal cardiac surgery [22]. In our patient some risk factors of fungal infection were found. The boy was prematurely born (gestational age 37 weeks) - with low body mass (2300g), with disturbances in the perinatal period (the prolonged therapy with antibiotics, and endotracheal intubation), with congenital malformation as evisceration which demands abdomen surgery. After the birth, the presence of bacteria and fungi in blood was found simultaneously. Our patient was given antibiotics in the neonatal period for a long time and in our opinion it is the main decisive factor for acquiring candidiasis.

The children with disorders characterised by immunocompromise (endogenous or exogenous) were more likely to have invasive candidiasis than the children with underlying competent immune systems [7]. Cytomegalovirus infection diagnosed in our patient could cause immunosuppression and become an additional factor influencing the development of invasive candidiasis.

Singer and Braunstein reported that there are many reasons that make the diagnosis of *Candida* infection difficult. These include: difficulty in the early isolation and identification of *Candida* species due to the slow growth of the organism and the dismissal of positive culture as contaminants [4, 20]. The diagnosis of invasive candidiasis would more likely have been missed in children with shorter periods of candidemia [7]. For efficacious treatment it is important to have an early diagnosis of systemic candidiasis [12]. Bayer et al. reported some poor prognostic factors, the most important of them is delay in diagnosis of more than 2 weeks after the onset of symptoms [3]. In our patient the delay in diagnosis was possible, because only two out of fourteen blood culture tests done were positive to fungi.

The risk of infective endocarditis is greatest in children with congenital heart diseases [9]. Our patient was born without any heart lesion.

FE most commonly involves the left side of heart (combined aortic and mitral, 70%) [9, 17]. Tricuspid valve endocarditis (TVE) occurs in 5-10% of cases with infective endocarditis [18]. The commonest causative agent of FE is *Candida albicans*, responsible for 24-46% of all FE [9, 13, 17]. In our patient there was a rare case of tricuspid valve FE due to *Candida albicans* since he was

without any predisposing cardiac abnormality or previous cardiac surgery.

Candida albicans is usually susceptible to Fluconazole but Amphotericin B is the recommended therapy of choice for *Candida albicans* infections [1]. The liposomal formulations of amphotericin B have achieved some success after conventional Amphotericin B failure. Six to eight weeks of therapy is recommended [9, 13, 16, 17]. Our patient was treated with Fluconazole and Amphotericin B (its liposomal formulation) for the first two and half months of his life. Despite that, invasive candidiasis and fungal endocarditis appeared.

Festekijan A. reported that blood cultures positive for the same Candida species in the same patient fewer than 30 days apart were considered as the same candidemia event [7]. In our patient negative blood cultures were obtained several times within 6 weeks before discharging him from hospital. Despite this, the boy was readmitted to the hospital with candidemia after 3 weeks at home. Because of that, it seems to be essential to extend the time of observation of patient with candidemia.

The case is presented because of:

1. A rare occurrence of infective endocarditis in infants without congenital heart disease
2. Great problems with the proper diagnosis of the disease (several repeated echocardiograms – without any abnormalities; only three of fourteen blood culture tests were positive to fungi)
3. Being an example of long-lasting antibiotic therapy complication, despite the simultaneous use of antifungal treatment.

CONCLUSIONS

1. Fungal endocarditis developed probably as a consequence of the prolonged broad spectrum antibiotics use and central venous line use, secondary to neonatal surgery
2. Fungal endocarditis had a subacute course and occured despite the long-term antifungal treatment of candidemia in the period when the child was considered healthy.
3. Because of that, it seems to be essential to extend the observation time of the patients with candidemia.

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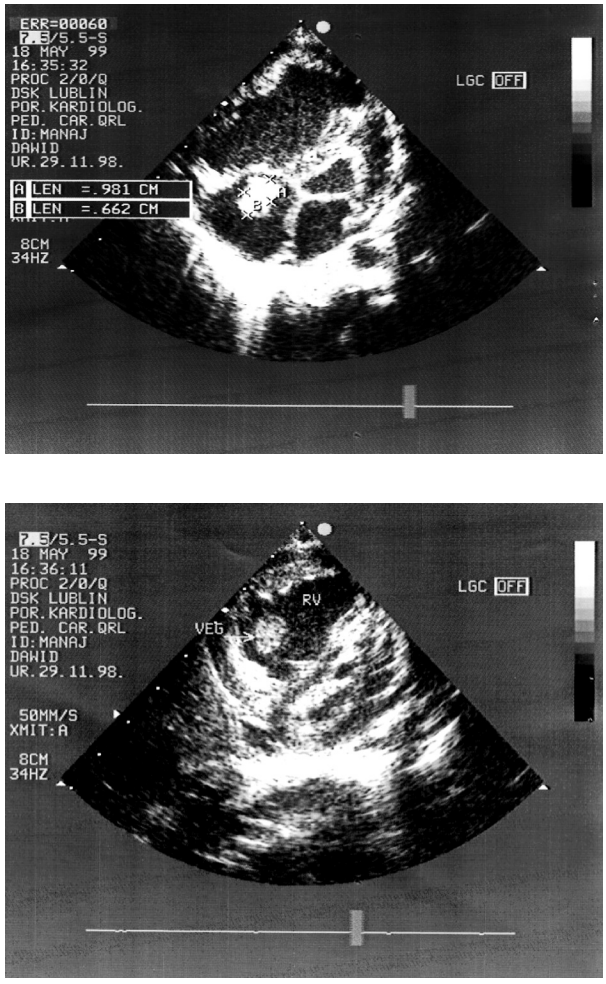

Fig. 1. Echocardiographic images

Table 1. The results of culture tests at the first hospitalization

Blood	Urine	Pharynx	Nose
2 x negative	1 x negative	Neisseria catarrhalis Streptococcus pneumoniae	Staphylococcus aureus
Candida albicans	Gram-negative bacteria 10^2/ml	Staphylococcus aureus	Staphylococcus aureus
Staphylococcus aureus Candida albicans	Gram-negative bacteria 10^2/ml	Neisseria catarrhalis Streptococcus pneumoniae	Neisseria catarrhalis
Micrococcus species	Candida albicans	Escherichia coli	
4 x negative	3 x negative		

Table 2. The results of culture tests at the second hospitalization

Blood	Urine
Candida albicans	4 x negative
4 x negative	