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NATIVE VALVE ENDOCARDITIS CAUSED BY METHICILLIN-RESISTANT *STAPHYLOCOCCUSEPIDERMIDIS* IN A PATIENT WITH ADVANCED LIVER CIRRHOSIS

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SUMMARY – We present a case of a 50-year-old man with advanced liver cirrhosis and native valve infective endocarditis caused by methicillin-resistant *Staphylococcus epidermidis*. Bacterial infections are one of the most common complications of liver cirrhosis, but reports of infective endocarditis in patients with liver cirrhosis are relatively rare. Because of vulnerability of patients with advanced cirrhosis for developing infections, it is necessary to pay attention to the pathogens that are sometimes considered contamination and actively seek for the seat of infection, even in less expected areas (e.g., native heart valves without a history of heart disease).

Key words: *Endocarditis, bacterial; Heart valve diseases; Liver cirrhosis, alcoholic; Methicillin resistance; Staphylococcus epidermidis; Case reports*

Introduction

Bacterial infections are one of the most common complications of liver cirrhosis, especially when it comes to decompensated liver cirrhosis[1]. The most common infections are spontaneous bacterial peritonitis, urinary tract infections, pneumonia, and cellulitis[1,2]. Reports of infective endocarditis in patients with liver cirrhosis are relatively rare[3]. The prevalence of infections is 25%-30% and they are responsible for 30%-50% of fatal outcomes in these patients[1]. Reduced clearance of bacteria, as well as changes in intestinal mucosa may potentiate bacterial translocation. Impaired infection defense in cirrhosis may also contribute to a decreased level of complement components, impaired function of macrophages, and decreased level of expression of HLA-DR on monocytes[1,4]. Blood stasis, the existence of shunts through peripheral collateral veins and portal hypertension may contribute to persistence of bacteremia, as well as a variety of endoscopic procedures, thus increasing the tendency to develop endocarditis[5,6].

In the absence of systemic inflammatory response syndrome (SIRS), a Model for End-Stage Liver Disease (MELD) score of >18 is associated with 12% in-hospital mortality, whereas in the presence of SIRS the mortality increases to 43%[7,8]. The frequency of isolation of multiresistant bacteria in patients with cirrhosis reaches 40% in some tertiary hospitals[7,9,10].

The incidence of infective endocarditis is approximately 2-6 cases *per* 100 000 people *per* year, and has not decreased over the last 30 years[11]. In the U.S., about 10 000 to 15 000 new cases of infective endocarditis are annually diagnosed on average, and according to a French study, the incidence is 33.8 cases *per* million[12]. Despite advances in medicine, mortality rates are still between 10% and 30%[11,13]. It is more common in people older than 60 years, men, injection drug users, related to poor dental hygiene and dental

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infections, patients with structural heart disease and those with artificial valves. It is also more common in patients with previous acute infective endocarditis, presence of an intravascular device, patients on chronic hemodialysis, and patients with HIV infection[12]. It has also been recognized that diabetes as a comorbidity in patients with infective endocarditis is an independent predictor of mortality[11,14].

Case Report

A 50-year-old patient with decompensated liver cirrhosis of ethylic genesis was admitted for pretransplantation screening. Cirrhosis was diagnosed six years before and the patient was hospitalized on three occasions in a regional hospital with encephalopathy as the leading symptom. Seven months before current hospitalization, right hallux redness appeared followed by elevated temperature up to 39 °C, with no trauma or injury of the skin. He was diagnosed with osteomyelitis and the hallux was amputated under local anesthesia. Three hours later, he suffered a minor cerebrovascular accident with left sided hemiparesis. After three days, he underwent computed tomography (CT) of the brain, which showed "a small lesion on the right". Approximately 2.5 months after the stroke, he underwent stationary physical rehabilitation. During the last weeks of rehabilitation, he felt low back pain accompanied with fever and two months before current hospitalization he was diagnosed with spondylodiscitis at L5S1. Vancomycin therapy was administered for three weeks. Several days before current hospitalization, he was hospitalized in a regional hospital due to encephalopathy and febrility up to 39 °C. Afterwards, he was transferred to our hospital.

At admission, the patient presented with fever (38.3 °C), blood pressure 130/85 mm Hg, heart rate 76/min; he was disoriented, dysarthric, with icteric skin, mucous membranes, and sclerae. His abdomen was distended with ascites, painless, with palpable spleen 1 cm. There was mild lower leg edema with trophic skin changes and slightly weakened strength of the left hand. Auscultatory examination of the lungs was normal and systolic diastolic murmur was heard over the precordium. Initial laboratory tests were as follows: E $3.24x10^{12}$/L, Hb106 g/L, Hct 0.301 L/L, MCV 92.9 fl, platelet $31x10^{9}$/L, L $5.98x10^{9}$/L, PT 0.46, INR 1.6, total bilirubin 180 μmol/L, AST 44 U/L, ALT 26 U/L, GGT 49 U/L, ALP 123 U/L, ammonia 62 μmol/L, creatinine 119 μmol/L, CRP 62.1 mg/L. MELD score was 18 and the classification of cirrhosis severity was Child Pugh C.

Given the above, the suspected diagnosis was infective endocarditis, which was confirmed by transthoracic and transesophageal ultrasound, which revealed mildly sclerotic mitral valve with floating vegetation at the top of the atrial side of the anterior

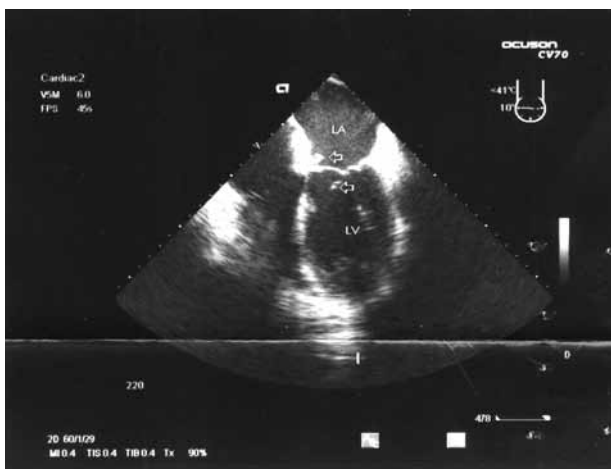

Fig. 1. Transesophageal ultrasound: mitral valve with floating vegetation at the top of the atrial side of the anterior mitral leaflet, with a thread-like formation on the edge of the same leaflet in the space of the left ventricle.

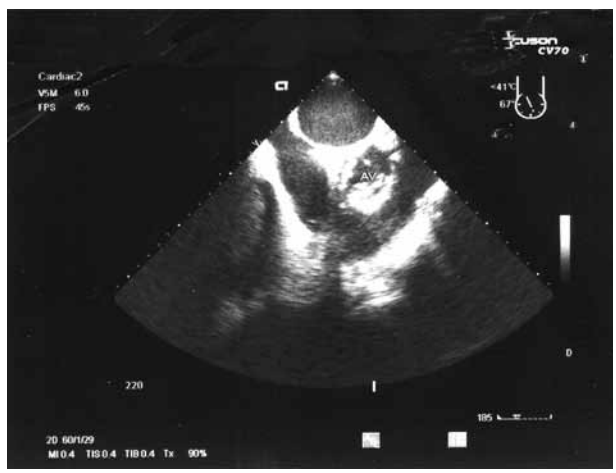

Fig. 2. Transesophageal ultrasound: all three aortic valve leaflets show thickening of endocarditic nature.

mitral leaflet, 1x0.4 cm, with thread-like formation on the edge of the same leaflet in the space of the left ventricle (Fig. 1) and with the presence of trivial mitral insufficiency. Also, in all three aortic valve leaflets, thickening of endocarditic nature (Fig. 2) was found with accompanying aortic regurgitation grade 2-3+. The left ventricle properly contracted with ejection fraction of about 65% and no regional disturbances in motility. Once coagulase-negative staphylococci and twice *Staphylococcus epidermidis* resistant to oxacillin were isolated from blood cultures. Urine culture was sterile and there were no signs of spontaneous bacterial peritonitis. Vancomycin was included in patient therapy.

On day 12 of admission to our institution, the patient developed left bundle branch block (LBBB) and then total atrioventricular (AV) block. A temporary pacemaker was embedded and inotropic and vasoactive support was introduced. The further course was complicated by intense abdominal pain. Ultrasound found splenic infarction followed by multiorgan failure with fatal outcome on day 16 of his stay in our hospital. In the post mortem reported tracheal aspirate, isolation of *Klebsiella pneumoniae* ESBL 10^4 CFU/mL and *Acinetobacter baumanii* (carbapenem-sensitive) ≥10^5 CFU/mL was reported. Autopsy was performed and revealed liver cirrhosis, ascites, endocarditis of mitral and aortal valve, pulmonary edema, right basal bronchopneumonia, intra-alveolar hemorrhage, and infarctions of the spleen.

Discussion

The best studied infectious diseases in cirrhotic patients are spontaneous bacterial peritonitis, pneumonia and urinary tract infection. Reports of infective endocarditis in patients with liver cirrhosis are relatively rare. Thus, in the study by Hung *et al.*[3], bacterial endocarditis during three years of monitoring was recorded in 0.3% of patients with cirrhosis, but compared with patients who did not have cirrhosis, patients with cirrhosis had a higher risk of developing bacterial endocarditis. In a study of 166 patients with infective endocarditis, 29% of them had chronic liver disease, and it was the most common comorbidity in the study group[11]. Chronic liver disease as a comorbidity in patients with infective endocarditis was found to be an independent predictor of mortality. Cirrhotic patients had a higher mortality (51% *vs*. 17.7%) and it was associated with the severity of liver disease[15].

Coagulase-negative staphylococci (CoNS) are the predominant bacteria that colonize the skin and therefore they are the most common bacteria that contaminate blood cultures. Blood cultures positive for these bacteria are typically considered by physicians to be clinically insignificant. The role of CoNS, including *Staphylococcus epidermidis*, as true pathogens is usually appreciated only in patients with prosthetic material[16].

Native valve endocarditis (NVE) has been considered primarily a community-acquired infection, although healthcare-associated cases are becoming increasingly common. CoNS were uncommon causes of NVE, but emerging association between NVE due CoNS and healthcare acquisition was validated in a large prospective multicenter investigation[17,18]. CoNS were responsible for 8% of NVE cases not associated with injection drug use, whereas 49% of cases were acquired in a healthcare setting. The same study found that the overall rate of methicillin (oxacillin)-resistant isolates among CoNS that caused NVE was 41%, 22% of which were community-acquired[17,18].

According to a retrospective study involving 757 patients with infective endocarditis, the average time from symptom onset to the initiation of antibiotic therapy was 52 days and the longest period was 489 days[19]. The incidence of embolism in patients with left-sided infective endocarditis in a study of 629 patients was 21% and 9.8% of patients had more than one episode. Among patients with embolism, 7.4% of them had central nervous system, 27.8% lower limb, and 5.3% spleen embolism[19].

The incidence of spondylodiscitis in patients with infective endocarditis according to different reports ranges from 5% to 15%[20,21]. In the study by Le Moal *et al.*[21], spondylodiscitis in all cases described was diagnosed prior to the diagnosis of infective endocarditis, was more common in men, and affected lumbar spine in 71% of cases.

According to another two studies[22,23] in patients with infective endocarditis, the incidence of cases of simultaneous involvement of mitral and aortic valve was approximately 12%. Although individual suc-

cessful cases have been described[24], valve replacement is performed less frequently in cirrhotic patients and operative mortality is extremely high in stage B and C patients. Due to the presence of severe hepatic dysfunction, cardiac surgery is often not undertaken even when indicated[15]. There was a case of simultaneous mitral valve replacement for acute endocarditis and orthotopic liver transplantation for end-stage liver disease[25].

We presented a rare case of a patient with advanced liver cirrhosis and native valve infective endocarditis caused by methicillin (oxacillin)-resistant *Staphylococcus epidermidis* (MRSE) with probably the first symptoms of embolism seven months before the diagnosis of endocarditis (osteomyelitis of the right leg, ischemic cerebrovascular accident, then spondylodiscitis at L5S1) and later spleen microembolism, total AV block, followed by the development of multiple organ failure and death. There were no history data indicating the possible entry points of infection (there was no information on endoscopic procedures or the presence of a central venous catheter), but considering that the patient had advanced liver cirrhosis and therefore impaired immunity, it was possible that only slight interruption of the skin continuity could lead to the introduction of resistant pathogens, probably in terms of hospital environment. There was no information on previous heart disease or valve disease or on the existence of cardiac murmur either. Vancomycin therapy for spondylodiscitis had been initiated two months before current hospitalization and lasted for 3 weeks, which probably helped a little, but also masked the clinical picture. At the time of the diagnosis of infective endocarditis, the patient had a high MELD score and active infection with a resistant microorganism, so the patient was not considered eligible for surgical treatment or liver transplantation.

Endocarditis in patients with advanced liver cirrhosis (Child Pugh score C) may be a therapeutic challenge. Vulnerability of patients with advanced cirrhosis for developing infections with no clearly visible entrance, and the pathogens that are sometimes considered contamination should lead to more active search for the seat of infection, even in less expected areas (e.g., native heart valves without a history of heart disease).

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Sažetak

ENDOKARDITIS NATIVNE VALVULE UZROKOVAN METICILIN-REZISTENTNIM SOJEM BAKTERIJE *STAPHYLOCOCCUS EPIDERMIDIS* U BOLESNIKA S UZNAPREDOVALOM CIROZOM JETRE

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Prikazujemo slučaj 50-godišnjeg muškarca s uznapredovalom cirozom jetre i endokarditisom nativne valvule uzrokovane meticilin rezistentnim sojem bakterije *Staphylocoocus epidermidis*. Bakterijske infekcije jedne su od najčešćih komplikacija ciroze jetre, ali su slučajevi infektivnog endokarditisa u bolesnika s cirozom jetre relativno rijetki. Zbog osjetljivosti bolesnika s uznapredovalom cirozom za razvoj infekcija potrebno je obratiti pozornost i na patogene koje ponekad smatramo kontaminacijom te aktivno tražiti mjesto infekcije, čak i u manje očekivanim područjima (kao što su nativne srčane valvule bez povijesti ranije srčane bolesti).

Ključne riječi: *Endokarditis, bakterijski; Srčani zalisci, bolesti; Jetrena ciroza, alkoholna; Meticilin, rezistencija; Staphylococcus epidermidis; Prikazi slučaja*