CASE REPORT

Oral Antibiotic Therapy for Infective Endocarditis Due to Enterococcus Spp. After Hemorrhagic Stroke and Heart Surgery

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Introduction

Infectious endocarditis (IE) is a severe infectious disease with an annual incidence of 3 - 7 cases per 100 000 people, and is considered the 3rd most life-threatening infection after pneumonia and intra-abdominal abscess.[1] Intra-hospital mortality ranges from 15 to 30%[2] and patients affected today are older and have more comorbidities than in the past. [3]

In IE the treatment is traditionally performed in hospitalized patients, due to the need for intravenous antibiotics. Patients with IE on the left side of the heart are typically treated for 2 - 6 weeks, according to the American and European Guidelines. [1-2] *Enterococcus* spp. is the third cause of IE, representing 10% of cases in non-users of intravenous drugs, and is considered to be a bacterium that is difficult to eradicate, requiring 6 weeks and the combination of antibiotics.[2]

The possibility of home or outpatient treatment is attractive from both a social and an economic point of view,[4] but it still finds resistance in clinical practice. We will present a case of infective endocarditis by *Enterococcus* spp. complicated with hemorrhagic stroke and need for cardiac surgery that used oral antibiotics after initial intravenous course.

Case Report

A 75-year-old white male, smoker, hypertensive, previous myocardial infarction with coronary stent in 2013, using 100mg of ASA, sought care for night sweats for 1 month, fever, loss of 8 kg, left flank pain and dyspnea on moderate efforts. He had tachycardia and tachypnea, cardiac auscultation with ++ / 4 diastolic murmur and + / 4 systolic murmur in the aortic area, and crackles on the right lung base. Cultures were collected and piperacillin-tazobactam associated with Furosemide was started. Examinations showed hemoglobin 11.3, Leukocyte count 5500, cells with a predominance of neutrophils and without deviation, Platelets 125 000, C-Reactive Protein 70 mg / dL (VR < 1mg / dL), Creatinine 1.25 mg / dL, HIV negative, and normal pancreatic enzymes and transaminases. Electrocardiogram showed sinus tachycardia, 1st degree atrioventricular block (AVB), and lower inactive zone. Contrast tomography of the abdomen reported abdominal lymph nodes of 1.2 cm and normal spleen. A transthoracic echocardiogram was performed with an ejection fraction of 55%, slight aortic regurgitation and left ventricle with hypokinesia of the basal segment of the inferolateral wall. There were 2 positive blood cultures for *Enterococcus* spp. sensitive to ampicillin and gentamicin**.** Transesophageal echocardiogram with aortic vegetation up to 7mm, confirming definite infectious endocarditis from 2 Major Criteria of Duke's Modified Criteria. Antibiotic replaced by ampicillin and ceftriaxone due to the renal dysfunction presented by the patient and his age. Negative control blood cultures after 48 hours, and improved inflammatory signs and dyspnea. Seven days after the start of the antibiotic, the patient presented motor incoordination in the L hand, performed magnetic resonance imaging (MRI) with the presence of a 27 mm lobar hematoma (Figure 1A) in the right post-central gyrus, without deviation from the midline. One week later he had paresthesia in the right upper limb and focal convulsion,

Keywords

Antibiotic Prophylaxis; Endocarditis, Bacterial; Enterococcus; Stroke, Cardiac, Surgery.

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MRI with subarachnoid hemorrhage (Figure 1B) between grooves of the frontal lobe on the left, opting for conservative treatment and carbamazepine. Hypothesis of hemorrhagic events secondary to septic emboli, transesophageal echocardiogram with vegetation of the same size and mild regurgitation was raised, as well as negative blood cultures. A few days later he developed acute kidney failure and acute lung edema, a new echocardiogram with severe aortic regurgitation, with increased dose of furosemide and vasodilators, besides an evaluation by a cardiac surgeon. He underwent emergency surgery with a Biological Aortic Valve. The excised valve was not sent for histopathology. In the surgical report there was a description of perivalvar abscess. After surgery, he had control of heart failure and recovery of renal function to baseline. The patient evolved with symptomatic 2:1 AVB and had definitive PM implantation. While a CBC showed lymphocytosis, a bone marrow biopsy confirmed chronic lymphocytic leukemia (CLL). Due to presenting RAI stage 0 for CLL, it was defined a conservative treatment by Hematology, without the need for specific therapy. Due to the worsening of valve dysfunction with adequate antibiotics, the day of surgery was considered the day 0 of treatment. After 16 days of intravenous ampicillin and ceftriaxone, there was migration to isolated ampicillin orally. Discharge occurred on the 18th day after surgery and the remainder of the treatment was completed at home, totaling 42 days after surgery. A review visit was performed at 2 weeks, and 2, 6, and 12 months after the end of the antibiotics, without clinical manifestations of congestion or infection, without murmurs, and with negative blood cultures. Repeated echocardiogram at 12 months showed biological aortic valve in normal operation and without vegetations. The patient underwent cerebral angiotomography at admission, as well as 2 months after discharge. The images were not compatible with mycotic aneurysm. He was accompanied by Neurosurgery and Neurology, requiring no neurosurgical intervention.

Discussion

Compared to patients with other types of IE, patients with IE due to Enterococcus tend to be older, have a higher prevalence of cancer, vegetation in the aortic valve, relapse, and a previous history of urinary and abdominal infection. Older patients with various comorbidities, including kidney failure as a limiter for the use of aminoglycosides, and the need for combined therapy to eradicate enterococcal infection makes the antibiotic treatment of IE by Enterococcus a challenge.[5] The atypical presentation is common in older adults or immunocompromised individuals. Our patient presented these two characteristics, being diagnosed with chronic lymphocytic leukemia on admission. In a Danish cohort of patients with IE, 11.8% of cases were

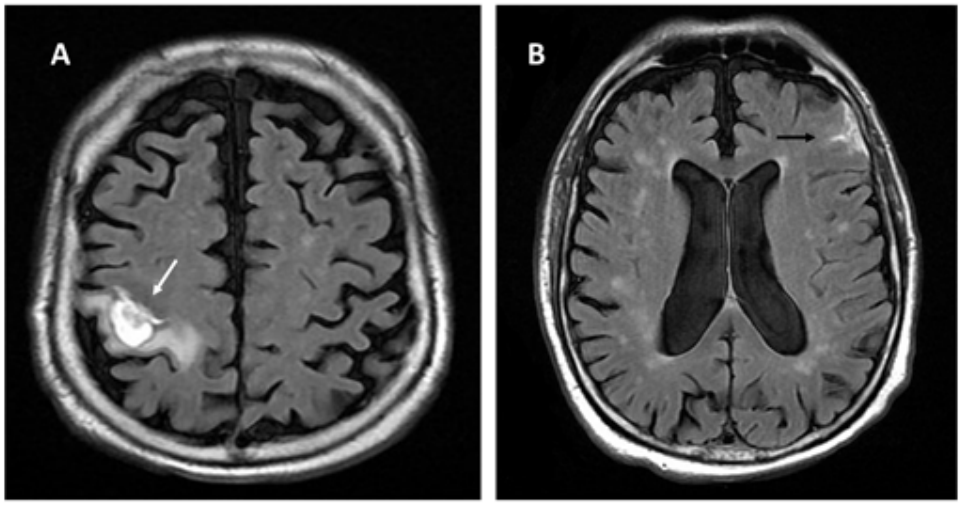

Figure 1 –Magnetic resonance imaging of the brain in the T2Flair sequence. Lobar hematoma (white arrow) in the right post-central gyrus (A) and subarachnoid hemorrhage (black arrow) to the left (B).

diagnosed with cancer in a 3.5-year follow-up, and the risk of a hematological neoplasm was 24 times higher in the first 3 months after the infectious diagnosis.[6]

Systemic embolization due to vegetations complicates from 22% to 50% of cases. Of these events, 65% involve the central nervous system (CNS), with ischemic stroke (CVA) being the most diagnosed.[2] In general, mitral vegetations are associated with a higher risk of embolization (25%) compared to those in the aortic valve (10%). [7] The size (> 10mm) and mobility of vegetations are independent predictors of an embolic event.[3] In a study including patients with IE in the mitral and or aortic valves, [8] the incidence CNS embolism after antibiotic initiation was of 12.9%, and 65% of these events occurred in the first 2 weeks of treatment. Our patient had hemorrhagic events, probably related to embolization, with 14 and 31 days of treatment.

After an IE-related hemorrhagic stroke, there is a tendency to postpone valve surgery, if indicated, for at least one month. [2] Garcia Cabrera et al.,[9] in a study of patients with IE in the left valves and hemorrhagic stroke, observed a mortality rate of 75% when the surgery was performed in less than 4 weeks after the hemorrhagic event compared to 40% after 4 weeks. The patient evolved with refractory heart failure, considered the main indication for surgery today,[1] and the decision was made to proceed with valve replacement surgery on the 6th day after the last hemorrhagic event, given the impossibility of postponing. Regarding the use of oral antibiotics, in a cohort of 426 cases with IE, 214 patients after initial intravenous treatment migrated to use of oral antibiotics, occurring on average 21 days after diagnosis of IE, and average of 28 days for *Enterococcus*, with amoxicillin being the medication chosen in 91% of these patients. The rate of relapse and reinfection in the oral treatment group was similar to that observed in intravenous treatment.[10]

In a multicenter randomized clinical trial of stable patients with aortic and/or mitral valve IE who used at least 7-10 days of intravenous antibiotics, participants were randomized for maintenance of intravenous treatment or migration to oral antibiotics. Approximately 38% performed heart surgery before randomization. The primary composite outcome of 6 months (all-cause mortality, unplanned heart surgery, embolic phenomena, or relapse) occurred in 12.1% in intravenous treatment and 9% in oral treatment (p=0.4), with the conclusion that migration to oral antibiotics was no less than the exclusive IV antibiotic. Enterococcus spp. corresponded to 25.4% of the cases that received oral treatment.[11]

Exclusive intravenous treatment imposes problems such as impaired venous network, risk of catheter-related infection and prolonged hospital stay.[10] In this reported case where the patient had a controlled infection, with negative control blood cultures, and where there was removal of site of infection by valve replacement surgery, it was possible to migrate to an oral antibiotic after an initial intravenous course, although Enterococcus is a difficult bacterium to eradicate. However, infectious endocarditis is a serious infection, and caution in antimicrobial treatment should be employed. Oral treatment has not yet been recommended by the American or European guidelines for endocarditis. [1,2]

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Sociedade Porvir Científico* under the protocol number 21406519.7.0000.5307. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Author contributions

Conception and design of the research: Pereira GAR. Acquisition of data: Pereira GAR; Kist GR; Machado TS; Barcellos CS. Analysis and interpretation of the data: Pereira GAR; Kist GR; Machado TS; Barcellos CS. Writing of the manuscript: Pereira GAR. Critical revision of the manuscript for intellectual content: Pereira GAR; Kist GR; Machado TS; Barcellos CS.

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