Difficulties in the treatment of infective endocarditis of unknown aetiology complicated by haemorrhagic stroke, cerebellum stroke, and spleen abscesses

Trudności w leczeniu infekcyjnego zapalenia wsierdzia o nieznanej etiologii powikłanego udarem krwotocznym mózgu, móżdżku i ropniami śledziony

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Słowa kluczowe: infekcyjne zapalenie wsierdzia, udar niedokrwienny mózgu, udar niedokrwienny móżdżku, ropnie śledziony.

Abstract

A 59-year-old man was admitted to the Rheumatology Department in order to conduct diagnostics of a hypoechogenic lesion located in the lower pole of the spleen. After 17 days of hospitalisation at the Department of Rheumatology and the Department of Neurology, the patient was referred to the Internal Medicine Ward due to a suspicion of advanced infective endocarditis. Seven days of antibiotic and antifungal therapy resulted in a reduction of C-reactive protein levels from 133.38 mg/l to 29.78 mg/l. Control echocardiography did not show progression of bacterial vegetation, but revealed an increase in the severity of bicuspid valve regurgitation. Following pharmacotherapy, on the 23rd day of hospitalisation the patient was transferred to the Department of Cardiosurgery and Transplantology at the Institute of Cardiology for urgent surgical treatment. After successful surgery the patient underwent physiotherapy, resulting in partial resolution of neurological symptoms. Currently, 2 years after the event, the patient remains in good general state. We therefore conclude that the IE Risk Index is of high clinical value.

Streszczenie

Mężczyzna 59-letni został przyjęty do Kliniki Reumatologii w celu rozpoznania zmiany hipoechogennej w obrębie dolnego bieguna śledziony. Ze względu na podejrzenie infekcyjnego zapalenia wsierdzia po 17 dniach leczenia w Klinice Reumatologii oraz Klinice Neurologii został przeniesiony na Oddział Chorób Wewnętrznych. Po 7 dniach farmakoterapii antybiotykami oraz lekiem przciwgrzybiczym nastąpiło zmniejszenie stężenia białka C-reaktywnego z maksymalnej wartości 133,38 mg/l do 29,78 mg/l. Echokardiograficznie nie stwierdzono progresji wegetacji, natomiast zwiększyła się niedomykalność zastawki dwudzielnej. Z tego powodu chory w 23. dobie hospitalizacji został skierowany ze wskazań życiowych na pilną operację do Kliniki Kardiochirurgii. Operacja przebiegła bez powikłań. Po 2-letnim okresie rehabilitacji częściowo ustąpiły porażenia i zaburzenia równowagi związane z udarami. Obecnie chory jest w stanie dobrym.

Introduction

The number of detectable neurological complications of infective endocarditis (IE) has been increasing in recent years and is estimated at 40–50%, about 30% of them being detected incidentally as a result of greater availability of diagnostic imaging of central nervous system (CNS) [1–3]. About 90% of embolisms affect the brain area that receives a blood supply from the middle cerebral artery [4]. Therefore, cerebellar strokes constitute less than 10% of all strokes.

Table 1. Formulas for calculation of the IE Risk Index (IR)

Mathematical formula of the Risk Index (IR)	$I_R = \frac{\text{CRP [mg/l]}}{\text{Hgb [g/dl]} - \beta} \times 10$, where β = 6 g/dl
The Risk Index 1 month before hospitalisation	$I_R = \frac{109.60}{13.9 - 6} \times 10 = 138.73$
The Risk Index on admission	$I_R = \frac{133.38}{10.3 - 6} \times 10 = 310.2$
The Risk Index on the 4th day of hospitalisation	$I_R = 485$
The Risk Index on the 20th day of hospitalisation	$I_R = \frac{29.78}{10.1 - 6} \times 10 = 72.6$

The most common neurological complication is cerebral stroke, while encephalopathy, central retinal artery blockage, mycotic aneurysms, abscesses, meningitis, and seizures occur less frequently [5, 6]. The following factors predispose to neurological complications of IE: heart failure, arrhythmias, abnormal atrioventricular conduction, and the presence of suppurative lesions [4].

Most complications occur as a result of the presence of bacterial vegetations, mainly involving mitral (about 25%) and aortic (10%) valves [7]. In the study by Anderson *et al.* [8], among patients with IE of the mitral valve, mortality in the acute phase of stroke reached 29% and 57% when vegetations were located on the aortic valve, with total mortality estimated at 35%.

An extremely interesting new observation requiring further research concerns the relationship between the number of platelets and the occurrence of thromboembolic events [9]. A positive correlation was demonstrated between the number of neurological complications and negative results of blood cultures. This is assumed to be a consequence of the prolonged diagnostic process in IE and empirical difficulties in selecting the effective drug therapy in such cases. Guidelines propose empirical antibiotic therapy with gentamicin and vancomycin [1, 2], and recently also tritherapy with the addition of rifampicin.

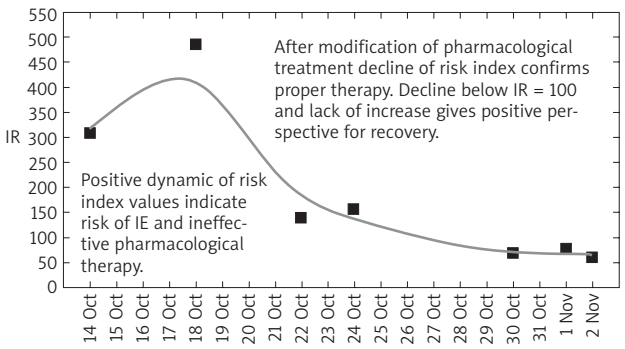

Figure 1. Changes in Risk Index (IR) values before and during treatment

We should not forget about the high effectiveness of cardiac surgery performed in a timely manner, i.e. after a week of ineffective empirical therapy, when vegetations show significant progression. Such a procedure is effective in reducing the number of neurological complications [10]. On the basis of the selected case we wanted to demonstrate the value of the IE Risk Index [11] as a prognostic factor and a diagnostic method facilitating selection of therapy, as well as serving to estimate the risk of complications. The following example is one of several cases proving the clinical usefulness of this index (Table 1, Figure 1).

Case report

A 59-year-old male with a history of hypertension and glaucoma was admitted to the Internal Medicine Department, presenting with pain in the lumbar spine radiating to the right buttock, weight loss, and fever. Abdominal ultrasound was ordered to elucidate the symptoms. Laboratory tests yielded abnormal results: C-reactive protein (CRP) – 109.60 mg/l, troponin – 0.30 ng/ml, creatine cinase MB (CK-MB) – 34 IU/l, urea – 69 mg/dl, and leukocytes – 16.4 × 10^3/µl, including 88% of neutrophils and 5% of lymphocytes, erythrocytes – 4.44 × 10^6/ml, haemoglobin (Hb) – 13.9 g/dl, heamatocrit (Ht) – 40.4%, D-dimer – 459.7 µg/l, and fibrinogen – 801 mg/dl.

A calculated Risk Index IR amounting to 138.73 indicated the relative risk for IE [11]. Ultrasound examination drew attention to the changes in the spleen. The measured longitudinal diameter of the spleen was 128 mm, and the lower pole of the area contained a hypoechogenic lesion 29 × 27 mm in size. All other organs were unremarkable. An X-ray of the spine displayed left-sided scoliosis, degenerative changes in the form of osteophytes located on the anterior and posterior vertebral edges, most pronounced on the inferior surface of L4-L5 and L5-S1 vertebrae, with apparent intervertebral space narrowing and possible damage to the intervertebral disc.

Due to fact that further tests were required, the patient was admitted to the Rheumatology Department.

Laboratory test results: CRP – 133.38 mg/l, troponin – 0.08 ng/ml, CK-MB – 21 IU/l, urea – 35 mg/dl, glucose – 136 mg/dl, leukocytes – 7.7 × 10^3/µl with 83.9% of neutrophils and 11% of lymphocytes, erythrocytes – 3.54 × 106/ml, Hb – 10.3 g/dl, Ht – 30.7%, mean corpuscular volume (MCV) – 86.6 fl, platelets – 110 × 10^3/µl, and D-dimer – 591 µg/l; results of iron tests were typical for anaemia of chronic disease (TIBC – 82 µg/dl, iron – 46 µg/dl, ferritin – 1120 ng/ml); liver function tests (AST, ALT, GGT) were within normal limits, TSH – 3.40 µIU/ml, and cancer markers (AFP, CEA, CA15-3, CA19-9, PSA) were unremarkable. HBsAg, anti-HCV, HIV-Ag/Ab – negative; serology for cytomegalovirus and toxoplasma yielded negative IgMs and positive IgGs in both cases.

The urine test was within normal limits. Chest X-ray showed left-sided pleural and pleurodiaphragmatic adhesions; no other focal densities were found. The left ventricle was enlarged and the aortic arch was slightly dilated. Abdominal computed tomography (CT) examination confirmed the presence of changes in the lower pole of the spleen, described as subcapsular, linear, and oval hypodense areas indicative of infarction. The liver was moderately enlarged (183 mm), without focal lesions. The patient received enalapril 2.5 mg twice a day (bis in die – BD) and amlodipine 5 mg once a day (OD) for treatment of hypertension, dorzolamide and latanoprost (glaucoma), tramadol 100 mg s.c. BD, and the following antibiotic therapy: ciprofloxacin 400 mg intravenous (IV) BD, and ceftriaxone 1 g IV BD. On the morning of the fourth day of hospitalisation, the doctor on duty noticed signs of a newly developed stroke: dysarthria, left-sided hemiparesis, anisocoria, cognitive impairment, and increased blood pressure – 150/70 mm Hg. Computed tomography examination did not reveal any fresh intracranial haemorrhages, although evolving ischaemic stroke was observed in the right middle cerebral artery (MCA) region, as were numerous post-infarction cavities in both hemispheres of the brain, cortico-subcortical scarring in the upper left cerebellar hemisphere, and a moderately enlarged cerebellar sulcus. A biphasic CT examination of the chest ruled out pulmonary embolism. The patient received heparin in therapeutic doses.

After 6 days in the Neurology Department, the patient was again referred to the Rheumatology Department where further tests were performed to rule out antiphospholipid syndrome. Infective endocarditis was also suspected, prompting a transoesophageal echocardiography examination. Laboratory testing was carried out for autoimmune diseases: p-ANCA, ANA – negative and the test for lupus anticoagulant showed low concentrations of LA. Echocardiography revealed: atrial cavity without any evidence of a thrombus, proper atrial blood flow, rather flaccid atrial septum with trace patent foramen ovale (PFO), proper motion of thickened aortic leaflets, a 7-mm-long echo entering the left ventricular outflow tract from the right side, possibly corresponding to a vegetation (or partially detached mitral valve leaflet), features of a large (+++) aortic regurgitation wave, mitral leaflets without signs of inflammation, normal width of thoracic aorta, with a small plaque present in the lumen of the arc. Unfavourable changes in the dynamics of IR index (increase from 138.73 on admission to 310.2 on October 14th and subsequently to 485.12 on October 18th – Figure 1) suggested infective endocarditis. Thus, antibiotic therapy was modified from ciprofloxacin and ceftriaxone to vancomycin 1000 mg BD and gentamicin 180 mg OD, respectively. Additionally, antifungal therapy was implemented – fluconazole 100 mg/day. Blood cultures were collected 6 times and all of the results were negative, including fungal cultures.

The patient remained in poor condition, with cognitive deficits, afebrile. He was therefore transferred to the Emergency Department for further evaluation and management. Sources of infection were sought; dental consultation was planned, although according to the relatives, the patient was under regular dental care. Another echocardiography examination showed progression of aortic regurgitation (++++).

After about 3 weeks of antibiotic therapy (2 weeks of treatment with ciprofloxacin and ceftriaxone (?) followed by 1 week of vancomycin and gentamicin) the results of laboratory tests were as follows: CRP – 29.78 mg/l, leukocytes – 7.4 × 10^3/µl including 67% of neutrophils and 21.5% of lymphocytes, erythrocytes – 3.38 10^6/ml, Hb – 10.1 g/dl, Ht – 29.7%, platelets – 291 × 10^3/µl, and D-dimer – 381.5 µg/l. Following a change in drug regimen the Risk Index of IE was further monitored (Figure 1, Table 1), and a sharp decline in the value of the index pointed to the appropriateness of antibiotic therapy.

As the infection was under control, the patient was urgently referred for surgery and transferred to the Institute of Cardiology in Warsaw for treatment of a large aortic regurgitation.

Discussion

In 5–20% of cases bacteriological examination fails to determine the aetiology of IE. In some cases, the pathogen can be determined by immunoenzymatic methods or polymerase chain reaction (PCR).

In clinical practice treatment of IE in the absence of a causative pathogen is extremely challenging even for an experienced cardiologist. In many cases, serious complications of IE may occur even with a reduction of clinical symptoms and inflammatory markers (CRP, leucocytosis, procalcitonin, ESR). Central nervous system infarction is one of the most serious complications, including rare cases of cerebellar stroke.

The greatest mortality due to neurological complications of IE is associated with vegetations located

on the aortic valve, and affects every fifth patient [8]. Clinical symptoms associated with stroke do not allow for conduction of efficient physiotherapy and a return to work.

Therapy of spleen abscesses is a big problem, since surgical treatment is recommended only in selected cases, as small abscesses can be treated conservatively, which is difficult with negative blood cultures.

Despite a low rate of detection of IE aetiology, the current guidelines do not suggest any indicators allowing for reliable assessment infection dynamics. There are also no markers to finally confirm the patient's recovery.

Indications for emergency or urgent surgery in IE are well known, but there is a large group of patients who develop serious complications in the course of pharmacotherapy, which worsen their prognosis [12].

Complications include not only strokes, but also the development of aortic abscesses in areas that are difficult to locate, as well as spleen abscesses, which may become the source of IE relapse, particularly in light of the fact that standards for their surgical treatment have not yet been developed [13].

In young people the early stage of the disease and early implementation of effective antibiotic therapy determine the reduction of the complication rate [14]. The proposed risk index is useful for clinical purposes primarily in patients without an identified pathogen when empirical treatment is administered. Consecutive CRP measurements and blood counts over 48 h combined with the patient's clinical condition may be used to assess whether empirical therapy would be effective [11]. The calculated IR was 310.2, indicating its dynamic growth and progression of infection. The haemoglobin value in the denominator of the IR amplifies the changes of index values. A dynamic fall of the IR will point to correct pharmacotherapy. This index is also applicable in mixed infections. In such cases, even selection of the appropriate antibiotic according to the antibiogram may not produce a full clinical effect [15]. Additional antibiotic should be administered empirically according to the risk index and quickly checked for effectiveness. In patients with splenic abscesses the IR helps to identify patients who need urgent splenectomy [16, 17].

In the described case the risk index was used as:
– a diagnostic factor that facilitates selection of therapy – a change of antibiotic therapy with an observed increase in the IE IR,
– a prognostic factor and a parameter approximating the risk of complications – a dynamic fall and IR value remaining below 100 (Figure 1).

The high values (over 100) of the IR indicates risk of mortality in IE and ineffectiveness of pharmacotherapy.

A decline in the IR after modification of pharmacotherapy indicates adequate treatment. Decline in IR (under 40) and subsequent stabilisation is a predictor for recovery [11].

Conclusions

We presented a case of a patient with IE and a rare neurological complication, such as cerebellar stroke. Empirical treatment was not effective due to the lack of possibility of early application of the IR.

Conflict of interest

The authors declare no conflict of interest.

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