

SUMMARY

SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY OPPORTUNISTIC PATHOGENS – CASE REPORT

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Subacute infective endocarditic (IE) is not very common disease, but it must be considered in a patient with significant valvular heart disease and a persistent unexplained fever, in the intravenous drug abuser with fever, or in the young patient with an unexpected stroke, or subarachnoid hemorrhage. The development of a new regurgitates murmur which is indicative of an active endocardial process, must raise the possibility of IE.

This case report is about 66 years old male patient Z.P. with aortic valve insufficiency (AR) 3+ and mitral valve insufficiency (MR) 2+ with verified IE caused by opportunistic pathogens Gram-positive Enterococci after disuric problems. The main thing in this case, as it was described in relevant medical literature, was a progressive development of high-level resistance to antibiotics (amoxicillin with clavulonic acid, ampicillin, ciprofloxacin, gentamicin and vancomycin) and two major complications of IE – splenic abscess and stroke that is, probably, a result of massive intracranial hemorrhage.

Despite the treatment (antimicrobial therapy, splenectomy before planned aortic and mitral valve replacement and symptomatic therapy of coexisting heart failure, hypertension and heart rhythm disorders) patient had a stroke with consecutive respiratory and cardiac arrest. Even all measures of CPR were done, he died.

It means, if there is a bacterial IE caused by opportunistic pathogens sensitive on small number of antibiotics and/or that pathogens have progressive development of high level resistance to previously effective antimicrobial therapy, there is a large probability of two major complications (splenic abscess and stroke). These complications are usual cause of death, despite the doctrinaire treatment.

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Infective endocarditic (IE) is the condition in which there is infection of the endothelial surface of the heart caused by different microorganisms.

The characteristic lesion is the vegetation, variably sized amorphous mass of platelets and fibrin in which abundant microorganisms and scant inflammatory cells are enmeshed. Infective process most commonly involves heart valves, but infection may occur at the site of sepal defect, on chordae tendineae or mural endocardium.

Infection arteriovenous shunts, arterioarterial shunts (patent ducts arteries), or coarctation of the aorta are an endarteritis, but clinically and pathologically are similar to IE.

Acute IE is condition with marked systemic toxicity, in which there is valvular destruction or metastasis infection within few days to several weeks.

Subacute IE is condition that lasts many weeks to months with only modest toxicity and rarely causes metastasis infections. Subacute IE is mostly caused by *Stir. viridians*, enterococci, coagulate negative staphylococci or gram-negative coccobacilli.

Clinically, IE is classified on: native valve endocarditic (in children/in adults), intravenous drug abusers IE, prosthetic valve endocarditic.

Major criteria for IE diagnosis are:

- 1) positive blood culture

2) evidence of endocardial involvement

- oscillating intracardial mass, on valve or supporting structures
- vegetations on implanted prosthetic material
- abscess
- new partial dehiscence of prosthetic valve
- new valvular regurgitation (increase or change in preexisting murmur)

Minor criteria for IE diagnosis are:

- 1) predisposition (valvular heart disease and/or intravenous drug use)
- 2) fever $\geq 38.0^{\circ}\text{C}$
- 3) vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctiva hemorrhages, Janeway lesions)
- 4) immunological phenomena
- 5) positive blood culture with coagulate-negative staphylococci or microorganisms that not cause IE
- 6) serologic evidence of active infection with microorganism consistent with IE
- 7) Echocardiogram consistent with IE, but without major criteria.

IE clinical diagnosis:

- 1) positive 2 major criteria
- 2) positive 1 major and 3 minor criteria
- 3) positive 5 minor criteria

CASE REPORT

Patient Ž.P., 66 years old, was admitted with fulfilled criteria for subacute infective endocarditis existence: echocardiographic verified vegetation on aortic valve, two positive blood cultures (gram-positive enterococci), echocardiographic verified MR 2+ and AR 1+, fever upon 39°C and positive inflammation syndrome.

Subjectively: weakness, loss in weight and fever.

Anamnestic: About two months before admission to a local health center he had disuric disorders followed by fever, and because of that, he was treated by antibiotics and, few weeks after antibiotic therapy was high febrile again.

In youth he had frequent anginas, but without data about rheumatic fever, he was hypertensive many years ago with bad blood pressure regulation; about thirteen years before hospitalization a heart rhythm pacemaker was implanted to him. During hospitalization in local hospital he was treated by Ciprofloxacin and Amoxicillin with clavulonic acid, according to antibiogram and after treatment he showed an improvement in general condition, decrease of blood fibrinogen values and decrease of body temperature and one sterile blood culture was verified also. In that period of time patient had a paroxysm of supraventricular tachycardia that was treated by cardiotonic drugs.

In admission, patient was conscious, oriented, subfebrile, pale, eupnoic. Auscultative finding on lungs showed diffuse sharpen vesicular sound with bothsided (dominant right) inspiratory rales. Heart rhythm was absolute irregular, heart sounds were silent, systolic murmur on ictus was present and aortic murmur with propagation toward carotide arteries was present too, heart rate was about 70 beats per minute, arterial blood pressure value was about 135/90 mmHg. Liver and spleen were not palpable, kidneys were not painful during percussio. Pretibial edema were not present.

ECG on admission showed atrial fibrillation with absolute ventricular arrhythmia, left axis deviation. During hospitalization pacemaker rhythm was registered sometimes, and VES were often present but regressed after therapy with antiarrhythmic agents.

Laboratory findings showed accelerated erythrocyte sedimentation rate to 60mm in first hour, anemia - blood hemoglobine 107g/l, hematocrit-0.35, normal white blood cells number – $6.4 \times 10^9 /l$, trombocytopenia - $175 \times 10^9 /l$, increased values of blood urea nitrogen-8.9 mmol/l and creatinine 132 mmol/l, fibrinogen- 3.89 g/l. Other laboratory values were normal. Blood cultures were sterile in three blood samples. Candida species fungi were isolated in small number from urine samples, but were no significant for urinary infection existance.

Signs, specific for infective endocarditis existance including visible vegetation on non-coronary and left coronary leaflet of aortic valve, and rupture of non-coronary leaflet were verified by echocardiographic examination. Front mitral leaflet was thicker, and suspect vegetation on «jet» lesion was present. In dilated left ventricle (EDD: 7.1- 7.5 ESD: 4.1- 4.9 cm), showing signes of volume load, aortic regurgitation 3+ was registered. In dilated left atrium (5.0 cm) mitral regurgitation was registered. EF was

59%, and FS-32%. Right cardiac cavities were not dilated, pacemaker sond was visible and tricuspidal regurgitation tray also.

After one and half months, control echocardiographic examination was performed, and it showed vegetation existance on non-coronary aortic leaflet dimensions 10x2 mm, prolapsing in exit tract of left ventricle during dyastolic phase of heart contraction.

Abdominal echotomography was performed twice. Examination showed increased liver dimensions to 16 cm, liver was not homogenous, was without focal inclusions, dimensions of spleen were normal with focal structure that was verified in upper pole of spleen dimensions 35x30 mm, by echotomographic features seemed to be splenic abscess.

Intensive antibiotic treatment, according to antibiogram was performed in this case, due to the positive blood cultures from the start (Ciprofloxacyн, Amoxycillin), as well as empiric antibiothic therapy for gram-positive enterococci (Vancomycin, Gentamicyn).

After a treatment patient showed significant improvement in general condition, but subfebrile temperatures existed and because of that splenectomy was indicated. During a surgical procedure, 20.0 ml of purulent fluid was evacuated, and gram-positive enterococci were isolated from cultures made of it.

After splenectomy, patient was continuously febrile, worsen general condition despite using maximal dayly doses of antibiotics, with threatening heart failure. Surgical implanting of prostetic mitral and aortic valve was planned, but, stroke - another complication of bacterial endocarditis, showed up with rightsided eyes deviation, and that event was followed by respiratory an cardiac arrest. Despite all CPR procedures it ended letaly.

DISCUSSION

About two months after, probably not good enough treated urinary infection, infective endocarditis, caused by enterococcus - famous opportunistic pathogen resistant to antibiotics, was diagnosed in patient. Since the start of 20 th century, these microbes were known as infective agents causing IE and urinary infections.

Soon after start using penicillin in therapy, since fourth decade of 20 th century, it was discovered that results of antibiotic treatment in cases of infective endocarditis

caused by enterococcus were poor compared with cases of infective endocarditis caused by streptococcus, indicating small sensitivity of enterococcus to this specific antibiotic.

As Ampicyllin was synthetised, it was proven that minimal inhibitory concentration (MIC) of this antibiotic is for about one half smaller compared with MIC of penicillin for enterococcus. Despite that, it was observed that these infective agents, in very short period of time become resistant to this β -lactam antibiotic too, so β -lactam antibiotics, used as monotherapy, are not efficient enough. Neither one of other antibiotics is efficient like Penicilline and Ampicilline, because of the fact that enterococci are hereditary resistant to Cephalosporines, antistaphilococcus Penicillines, small concentrations of Clindamicyne, aminoglycoside antibiotics and (in vivo) Trimetoprim.

The conclusion is that choice therapy for IE caused by Enterococcus is Penicilline or Ampicilline, and in case of allergy reaction to these antibiotics or enterococcus resistance, Vancomycin is recommended combined with aminoglycoside antibiotics. In case of enterococcus resistance to these antibiotic too, further therapy is impossible. Despite all side effects of Streptomicyne and poor in vivo therapy results, because of synergistic bactericide effect of Streptomicyne and Penicilline, this combination is recommended too.

Except general symptoms of infection, which are mediated by cytokines, the clinical manifestations of IE result from:

1. the local destructions (due to intracranial infection)
2. the embolisation of non-infective or septic fragments of vegetations to distant sites, that results in infarction or infection
3. the hematogenous dissemination out of focus during continuous bacteriemia
4. the antibody response to the infecting microorganisms with subsequent tissue injury due to deposition of preformed immune-complexes or antibody-complement interaction with antigens deposited in tissues.

The symptoms and signs of IE are:

- a) *fever* (with rarely exceeded 39,4°C; fever may be absent or minimal in the elderly or in those with congestive heart failure, severe debility, or chronic renal failure and occasionally in patients with native valve endocarditis caused by coagulate-negative staphylococci)

- b) *heart murmurs* (are noted in 80-85% of patient with native valve endocarditic and are predisposing factors to IE; murmurs are commonly not audible in patients with tricuspid valve IE; the new or changing murmurs are frequent in patients with congestive heart failure, patients with chordate tendineae rupture...)
- c) *enlargement of the spleen* (it is noted in 15-50% of patients and it is most common in subacute IE)
- d) *peripheral manifestations are*
- *petechiae* on palpebral conjunctiva, the buccal and palatal mucosa, and the extremities
 - *splinter or subungual hemorrhages*
 - *Osler's nodes* – small, tender subcutaneous nodules that develop in the pulp of the digits or occasionally more proximally in the fingers and persists for hours to several days
 - *Jeneey lesions* – small erythematous or hemorrhagic macular non-tender lesions on the palms and soles and are the consequence of septic embolic events
 - *Roth spots* (oval retinal hemorrhages with pale center)
 - *musculoskeletal symptoms* – arthralgias and myalgias with inflammatory synovial fluid findings or prominent back pain due to metastasis infection in vertebral body or disc space
- e) *Systemic emboli* occurs in up to 40% of patients and are frequent subclinical events; the most frequent systemic emboli are: embolic spleney infarction (left upper quadrant abdominal pain, left shoulder pain, small left pleural effusion) and renal emboli (asymptomatically or with flank pain, hematuria, renal dysfunction), Transmural infarction due to coronary artery emboli, emboli to the extremities, mesenteric artery embolism and embolic occlusion of a central retinal artery, in less than 3% of all cases
- f) *neurological symptoms* occur in 30-40% of patients with IE: stroke in 15-20% patients with IE, intracerebral hemorrhage and subarachnoid hemorrhage; hemorrhage is most frequently caused by rupture of mycotic aneurysm and rupture of arteries due to septic arthritis, but also there are hemorrhages into an infarct caused by septic emboli and symptoms due to, for example, cerebritis

- g) *congestive heart failure* is primarily the result of valve destruction or rupture of chordae tendineae, but intracardiac fistulas, myocarditis and coronary artery embolisation may contribute to the genesis of congestive heart failure
- h) *Renal insufficiency* occurs in 15% of patients with IE; it is result of immune complex mediated glomerulonephritis, but it may be the consequence of nephrotoxic therapy (amino glycosides) and interstitial nephritis, too; focal glomerulonephritis and renal infarcts cause hematuria but rarely result in azotemia.

The most frequent extracardial complications of IE are splenic abscess and mycotic aneurysm

Splenic abscess occurs in 3-5% patients with IE. It most commonly occurs in patients with IE caused by Staph. aureus and gram-negative bacilli. It can be identified by ultrasonography and CT (but these tests usually can not discriminate between abscess and infarct). If there is passive enlargement of the lesion during antibiotic therapy, it suggests that it could be an abscess, and that can be confirmed by percutaneous needle aspiration. The therapy requires drainage (by percutaneous placement of a catheter) or splenectomy (if there are multiple abscesses or if the percutaneous drainage is not successful). Splenic abscess should be treated prior to valve replacement operation, to stop the dissemination of the infection, as it has been done in patient Z.P.

Mycotic aneurysm occurs in 2-5% patients with IE (in 1-5% there is aneurysm of cerebral vessels; most frequently is the aneurysm of the middle cerebral artery). It can be identified by angiography, and we have to think on mycotic aneurysm in any case of existing neurological symptoms. Many patients with IE, who have mycotic aneurysm or septic arteritis as a first symptom, get devastating intracranial hemorrhage, that was probably in our patient, considering to bulbar deviation in to the right side and suddenly respiratory arrest, and consecutive cardiac arrest. But, on mycotic aneurysm should be thought in conditions with focal deficits from embolic events and persisting focal headache, too. Surgical treatment is recommended for a single lesion that is not resolved during antimicrobial therapy. Sometimes, stable aneurysms may rupture after of completion of antimicrobial therapy, and recommendations for surgical interventions are arbitrary. Sergeants suggest that

surgical treatment should be considered in any case, if it is not going to cause serious neurological signs.

LITERATURE

1. Karchmer W.A.: Infective endocarditis. In Braunwald Heart Disease, 5th Ed, W.B. Saunders Company, Philadelphia, Pennsylvania, 1997;1077-99.
2. Murray E.B.: Vancomycin-Resistant Enterococcal Infections. N Engl J Med, 2000;342:710-721.
3. Shannon R.P., Rose G.A., Nickleit V. Case 1-1996— A 69-Year-Old Woman with Severe, Persistent Congestive Heart Failure after Treatment for Bacteremia. N Engl J Med, 1996;334:105-111.
4. Assembling a Coherent Story. N Engl J Med, 1994;330:48-50.
5. Gold H. S., Moellering R.C.: Antimicrobial – Drug Resistance. N Engl J Med, 1996;335:1445-53