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Title: Tricuspidal valve endocarditis due to *Yersinia enterocolitica*

Short title: *Y. enterocolitica* tricuspidal valve endocarditis

V. Krajinović, M.D., A. Tambić Andrašević, M.D. PhD, B. Baršić, M.D., PhD

University hospital for infectious disease “Dr. Fran Mihaljević”

Mirogojska cesta 8

HR-10000 Zagreb, Croatia

vladimir_krajinovic@yahoo.com

Corresponding author:

Vladimir Krajinović, MD

University hospital for infectious disease “Dr. Fran Mihaljević”

Mirogojska cesta 8

HR-10000 Zagreb

Croatia

Phone: +385 1 4603 253

Fax: +385 1 46 78 235

e-mail: vladimir_krajinovic@yahoo.com

CORRESPONDENCE

Yersinia enterocolitica is a gram-negative coccobacillus acquired by humans via oral route. It is associated with a wide spectrum of clinical and immunological manifestations, responsible for digestive diseases, including enterocolitis and mesenteric adenitis, as well as extra-digestive manifestations including respiratory tract and urinary tract infection, osteo-articular infection, erythema nodosum and endocarditis [1]. Bacteremia and sepsis are most often reported in patients with predisposing underlying disease, such as an iron-overloaded state (haemochromatosis, acute iron poisoning), immunosuppressive therapy, diabetes mellitus, alcoholism, cirrhosis or malnutrition. It is associated with a high mortality of 25 to 50% [2]. Infective endocarditis (IE) is a rare manifestation of *Yersinia enterocolitica* infection. Only 15 cases of *Yersinia enterocolitica* endocarditis have been published so far.

A 75-year-old man was admitted to our hospital because of high fever accompanied by chills and rigors that lasted for 7 days before admission. On the second day of high fever he felt pain and swelling of the left lower leg. The patient was in his usual state of health except for a medical history of arterial hypertension treated with amlodipine and cilazapril. A history of eating imported fish from Norway was recorded. On clinical examination his temperature was 38.2 °C, blood pressure 160/90 mm/Hg, and his pulse rate was 106 beats/min. The heart rhythm was regular and a grade 3/6 holosystolic ejection murmur was heard at the apex. Left lower leg and foot

were edematous and Homan's sign was positive. The patient felt no pain in the abdomen. Hematocrit was 48%, leukocytes 20900/mm³ with 91% neutrophils, platelets 199000/mm³, ESR 74 mm/h and urine analysis was normal. Glucose levels were normal. Total bilirubin was 42.8 µmol/L (direct 20.2; indirect 22.6), SGOT 72 U/L, SGPT 169 U/L, γ-GT 328 and alkaline phosphatase 372 U/L. The chest X-ray was normal. Electrocardiogram suggested left atrium and left ventricle hypertrophy. Ultrasound examination revealed multiple gallstones and calculosis of both kidneys. Three sets of blood cultures were taken and therapy with amoxicillin/clavulanic acid 1.2 g q8h IV plus gentamicin 240 mg once daily was initiated. Stool culture was negative but only on MacConkey and XLD agars. All blood cultures (BacT/ALERT FN and BacT/ALERT FA) were positive for *Y. enterocolitica*, serotype O:3. Current NCCLS (CLSI) guidelines were used. The strain was susceptible to amoxicillin (MIC 0.19 µg/ml), cefuroxime (MIC 1.5 µg/ml), ceftriaxone (MIC 0.047 µg/ml), imipenem (MIC 0.047 µg/ml), amikacin (MIC 1.5 µg/ml), netilmicin (MIC 0.75 µg/ml), gentamicin (MIC 0.75 µg/ml), ciprofloxacin (MIC 0.012 µg/ml), trimethoprim sulfamethoxazole, piperacillin and cefoperazone. Cardiac murmur suggested possible infective endocarditis. A transthoracic echocardiogram revealed a tricuspidal valve vegetation 5 mm large near the septal cusp with mild regurgitation. The patient was treated with ampicillin 2.0 g IV q6h for 19 days plus gentamicin 240 mg once daily for 14 days. Defervescence occurred after 7 days of treatment. Maculopapular rash appeared on day 19 suggesting allergy to ampicillin. The treatment with ampicillin was changed to ciprofloxacin 400 mg IV q12h for the next 23 days. The liver parameters normalised four weeks after admission.

Echocardiography on day 37 showed organization of the vegetation on tricuspidal valve with same level of regurgitation. No relapses were observed during the 26 months of follow up.

Yersinia enterocolitica is a rare cause of infective endocarditis. Among 1779 patients with IE included in the International Collaboration on Endocarditis – Prospective Cohort Study [3] this is the only case of *Yersinia* endocarditis (Correy R, personal communication). This is the first case of any native tricuspidal valve involvement without previously implanted pacemaker or known valvular disease and concomitant septic phlebitis. Only one patient had previously been reported with tricuspidal valve endocarditis but it was associated with contamination of previously implanted pacemaker [4].

Except for age, no other predisposing factors for *Yersinia* bacteremia were present in our patient. We assume that deep septic phlebitis is a consequence of gut-origin septicaemia with *Y. enterocolitica*. Right-side endocarditis suggests that septic phlebitis was primary infection. Conservative treatment with ampicillin and subsequent ciprofloxacin was successful and there was no need for valvular replacement. Concomitant treatment included heparin followed by warfarin for deep venous thrombosis.

Available data on twelve of fifteen previously reported patients with yersinial IE are presented in Table 1. Acute presentation affecting the mitral valve was recorded in 3 patients, aortic valve in 2 patients or both valves in 1 patient. Native valve endocarditis dominated with only two cases of prosthetic valve endocarditis. Multiple blood cultures were positive in all patients. Three patients died of septicemia and one of them had liver failure. All three patients

had mitral valve vegetations and autopsies confirmed the presence of valve vegetations.

The possibility of endocarditis should be taken into account in all patients with several positive blood cultures. Similar cases were reported by Appelbaum et al. [5] and Karachalios et al. [6]. Most of the published studies report that endocarditis due to *Y. enterocolitica* was treated with β -lactams and/or aminoglycosides [7, 8]. Our patient was successfully treated with a combination of ampicillin and gentamicin but because of an adverse event, the therapy was changed to ciprofloxacin as a single antibiotic regimen.

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Table 1. Clinical characteristics and laboratory findings in 13 cases of *Yersinia enterocolitica* endocarditis

Case Number	Reference	Age (years)/Gender	Clinical presentation	TTE	Positive/ total blood cultures	Therapy	Outcome
1	10	68 /M	Fever, right hemiparesis, brain, liver and spleen infarcts	No data	Unknown	Gentamicin	died of septicemia (2cm vegetation on MV histologically confirmed)
2	11	72 /M	Fever, chills	Mitral valve vegetations	7/7	Ampicillin + gentamicin	died of septicemia (vegetations on MV and abscess on mitral ring)
3	5	73 /M	Fever, myalgia, vomiting, septic skin infarcts	Aortic valve vegetations	2/2	Tobramycin	recovered
4	2	61/M	Unknown	Aortic valve vegetations	Unknown	Doxycycline, gentamicin, trimethoprim- sulfamethoxazole	recovered
5	12	58/M	Fever, jaundice, liver failure	No vegetations	3/3	Ampicillin, followed by cefuroxime + gentamicin + metronidazole	died of septicemia and liver failure (vegetations on MV histologically confirmed)
6	13	72/M	Fever, diarrhea, spleen, liver and bone infarcts	Mitral and aortic valve vegetations	6/6	Cefoxitin	recovered
7	14	74/ F	Fever, weakness	No vegetations	4/4	Ceftizoxime	recovered
8	4	56/M	Fever, diarrhea, left hemiparesis, brain infarct	No vegetations	5/6	Ceftriaxone + gentamicin	recovered
9	7	45/M	Fever, nausea, vomiting spleen infarct	No vegetations	3/3	Cefamandole + tobramycin, then imipenem and finally ceftriaxone	recovered (fibrinous vegetations on posts and ring of removed valve; no histology done)
10	8	68/M	Fever	Mitral valve vegetation	3/3	Ciprofloxacin + netilmycin	recovered
11	9	89/M	Fever with skin lesions	Tricuspid valve vegetation	3/3	Ceftriaxon + ofloxacin	recovered
12	6	58/M	Fever, malaise, ecchymoses	Mitral valve vegetations	3/3	Netilmycin + ofloxacin	recovered
13	(present case)	75 /M	Fever, chills, rigors, deep venous thrombosis	Tricuspid valve vegetation	3/3	Ampicillin + gentamicin then ciprofloxacin	recovered

M = male; F = female; MV = mitral valve; TTE = transthoracic echocardiogram