The importance of exposures in Culture-negative endocarditis in an IV drugs abuser

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Introduction

Infective endocarditis (IE) is a severe and life-threatening disease worldwide (1). However, because of non-specific clinical presentations, confirmation and prescription of effective treatment are sometimes not simple tasks. History may help significantly in the diagnosis of IE; for example, it is more common among drug addicts, particularly Intravenous drug users (2, 3).

Approximately 5% of IE cases have negative blood cultures (4, 5), and its risk factors are exposure to slow-growing bacteria such as Bartonella species, fastidious nonbacterial organisms, previous antibiotic use, underlying valvular heart disease, and intracardiac or vascular device or other foreign bodies in contact with the blood (6).

Most patients have nonspecific symptoms such as fever, fatigue, and weight loss. In a case series comprising 348 blood culture-negative endocarditis cases from France, almost all the patients had a fever as a presenting symptom. In contrast, about 50 to 70% had symptoms of heart failure, such as exertional dyspnea, and about 50% had insidious weight loss(9).

Bartonella spp. is a small, intracellular, gram-negative, and very fastidious rod mainly transmitted by vectors; they are the second most common cause of culture-negative endocarditis. Among the cases of Bartonella endocarditis, two species predominantly implicated in causing culture-negative endocarditis are B. henselae and B. quintana(7).

These bacteria have been isolated from many mammalian species, including cats and dogs. It can cause mild infection to severe and life-threatening endocarditis in humans and dogs. In dogs, several Bartonella species have been identified; one of the most common ones is B. henselae.

It should be mentioned that in recent years, more cases of culture-negative endocarditis have been reported from developing countries(8).

This report presents a case of a patient with culture-negative B. henselae endocarditis from Iran, diagnosed using a combined diagnostic approach that included clinical evaluation, imaging, epidemiology, serology, echocardiography, and transthoracic echocardiography (TTE).

Patient Information

The patient was a 38 years old male, single and unemployed with a history of addiction, who had received care from a treatment camp for six months. He was discharged when he was on methadone maintenance therapy just before his first hospital admission. He was an IV drug abuser with a history of regularly using

amphetamine, cocaine, and heroin. He also smoked cigarettes for 20 years. He also exposed that he had unsafe sex and lost contact with dogs and cats.

Clinical Findings Timeline

The symptoms onset was 20 days before admission when he had fever and chills besides shortness of breath in the camp. The patient was hospitalized in another care center for five days as a suspected COVID-19 case and he was treated with Remdesivir, but his nasopharyngeal and oropharyngeal COVID-PCR tests were negative. Having been discharged from the hospital, he started using amphetamine again, which deteriorated his condition.

This time he was admitted to our center, as a referral center, with severe dyspnea, high fever (40), chills, chest pain, myalgia, and hemoptysis. The patient was ill and, on physical examination, he had tachycardia (Heart rate=107) and tachypnea (Respiratory rate=28), with low blood pressure (90/60), fluctuated oxygen saturation which was less than 92%, normal heart auscultation, no clubbing, no splenomegaly, and no lymphadenopathy. Table 1 summarizes the lab results.

Table 1: the results of main lab tests at the admission time

WBC	18,100 (normal range between 4,500-11,000)
Procalcitonin	More than 30 (normal range between 0.5-5)
Covid PCR test	Negative
CRP	174 (normal range: Less than 10 mg/L)
Creatinine	1.1
Troponin	Negative
D-dimer	25.14 (normal range: less than 0.50)
Blood culture (3 times)	Negative
HCV Ab	Positive
HCV PCR	Negative

Diagnostic Assessment & Therapeutic Intervention

Due to fever, dyspnea, and an SPO2 below 90%, a Computed Tomography (CT) was performed. The chest CT showed moderate pleural effusion and bilateral emphysema in the apex of the lungs and cardiomegaly. Pelvic and abdominal ultrasounds were normal. Because of dyspnea, tachycardia elevated D-dimer, and SpO2 of less than 90%, we decided to take CT angiography for pulmonary thromboembolism (PTE). CT angiography showed PTE, moderate pleural effusion in the right lung compatible with empyema, and a blurred wedge in the left upper lobe (LUL). We put the patient under anticoagulation therapy with warfarin, after PTE was diagnosed, and based on the loculated pleural fluid in the CT scan, empyema pattern, and the patient's fever, the effusion was tapped, and a chest tube was placed. The patient's pleural fluid was analyzed, which was exudative with Alb=900, Pro=2400, LDH=1184, RBC=50, WBC=3400, Glucose=80, and negative culture.

The lung field was found to have a septic embolism pattern, which led to an echocardiogram. Upon echocardiography, small vegetation was detected; therefore, a transthoracic echocardiogram (TTE) was conducted to confirm. TTE showed severe tricuspid valve damage, 8 millimeter vegetation in place, increased pulmonary artery pressure (PAP= 40), and ejection fraction(EF)=45%, confirming the vegetation on the atrial side of the tricuspid valve.

According to the findings, the first diagnosis was right-side endocarditis, which led to septic embolism, so we started empiric antibiotic therapy with vancomycin plus ceftriaxone. After two weeks of constant fever despite broad-spectrum antibiotic therapy and pleural effusion drainage, we changed the antibiotic regimen to vancomycin plus meropenem, and, re-evaluated our diagnosis by taking a detailed history, re-sending blood cultures, which were negative 3 times, performing abdominal ultrasound and investigating the possible causes

of culture-negative endocarditis including Q fever, bartonella, and brucellosis, according to the history of staying in the camp. The serology and blood PCRs were sent to the laboratory of the Pasteur Institute of Iran. The PCR and serology for Q-fever were negative. serology wright and 2-ME test for brucellosis were negative, but a serology test confirmed for Bartonella henselae with a 1: 2048 titer.11the kit used was Bartonella IFA IgG.

In the meantime, we changed the patient's drug regimen to doxycycline (100 mg twice daily), instead of aminoglycosides, plus rifampin (300mg twice daily), due to the high level of creatinine (3-3.3 mg/dL), and warfarin was switched to enoxaparin due to rifampin and warfarin drug interactions and patient noncompliance.

After 72 hours he responded to this drug combination significantly; fever, tachycardia, and dyspnea improved, creatinine levels decreased and the pleural fluid test result was negative for Bartonella. After two weeks, rifampin was discontinued, but he received an extended course of doxycycline monotherapy. Also, due to severe tricuspid valve insufficiency, he underwent medical treatment, but because of his addiction, the cardiac surgery service did not recommend him for valvoplasty. A summary of the clinical practice of the patient is shown in Figure 1.

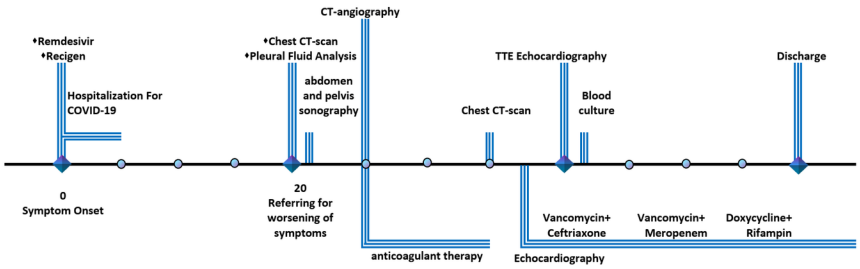

Fig 1. Timeline of symptoms onset & interventions.

Follow-up and Outcomes

After two weeks of treatment with doxycycline plus rifampin, clinically, the patient recovered with no difficulty in breathing and no chest pain. The results of the follow-up serology for B. henselae IgG were 1:512. The patient was discharged from the hospital approximately four weeks after admission, with a recommendation to visit a cardiologist, stop his IV drug abuse, and continue doxycycline and enoxaparin. A controlled chest X-ray showed improvement, and the chest tube was discontinued. The patient left the hospital in good general condition, without fever, with a normal heart rate and acceptable SpO2 (>94%).

Discussion:

Blood culture-negative IE has a high variation in prevalence among countries; the reports vary from 2.5- 70% of all infective endocarditis based on zoonotic agent exposure, antibiotic prescription pattern, and diagnostic tools (10).

Bartonella species are among the main microorganisms in culture-negative endocarditis. Meanwhile, among all 45 known Bartonella species, B. henselae is the second most common cause of culture-negative endocarditis(11). While cats and cat-scratch are considered the main reservoir of B. henselae, dogs could also transmit infection as accidental hosts(12).

Moreover, although Bartonella endocarditis is a worldwide issue and there are case reports from all parts of the world, most reported cases are from European countries and the Americas(11).

In this article, we are reporting a case of Bartonella endocarditis in Iran; it is notable that since Bartonella endocarditis is not common in Iran, usually physician does not put this agent on the list of their differential diagnosis, which causes several challenges to achieving a timely diagnosis and treatment of Bartonella endocarditis. Besides, the final diagnosis is even more challenging due to non-specific symptoms, which are the same as other subacute endocarditis or infective syndromes.

Moreover, the diagnosis is more challenging during the COVID-19 pandemic and the similarity between the typical symptoms of SARS-CoV-2 and endocarditis (13). Nevertheless, several diagnostic tools are available; despite their limitations, such as low specificity and cross-reactions, serology is still considered valuable in diagnosing Bartonella endocarditis(14). Also, PCR testing on whole blood or plasma specimen, with approximate sensitivity of 58% and specificity of 100%, is an effective diagnostic tool(15).

In this case, the patient had a history of contact with dogs, but based on previous studies, connection with cats is more common in most B. henselae endocarditis cases.

Moreover, in the current case, one of the first complaints of the patient was exertional dyspnea, and heart failure manifestations are considered an acute coronary syndrome. At the same time, based on the study conducted by Okaro et al., approximately 50 to 70% of Bartonella endocarditis presents symptoms of heart failure, including exertional dyspnea(11).

Low socioeconomic status is one of the underlying determinants of developing B. quintana endocarditis. While in our patient, who was diagnosed with B. henselae, the patient's social history regarding IV-drug abuse and low socioeconomic status were the most important considerations (11). Also, prognosis and treatment must consider epidemiological exposure and alternate diagnoses for culture-negative endocarditis in individuals who don't respond to therapy.

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S.Ghaderkhani, A.Seifi and E.Rahimi contributed to the conception and design of this report. The case was diagnosed and followed up by S. Sazgarnejad and S.Esmaeili. B.Haghdoost, A.Eghbal, M.Azaadbakhsh and S.Sazgarnejad participated in data collection. B.Haghdoost, A.Eghbal and M.Azaadbakhsh wrote the article. All authors contributed to data interpretation, critically reviewed the article and approved the final draft for submission.

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All authors have seen and approved the content of the manuscript and have contributed significantly to the work.

This study has been approved by the ethics committee of Tehran University of Medical. Sciences, adheres to the Declaration of Helsinki and informed consent was taken.

The patient has given a written informed consent for the publication.

The authors confirm that written consent has been obtained from the patient for submission and publication.

All the patient's data and materials are provided in the manuscript.

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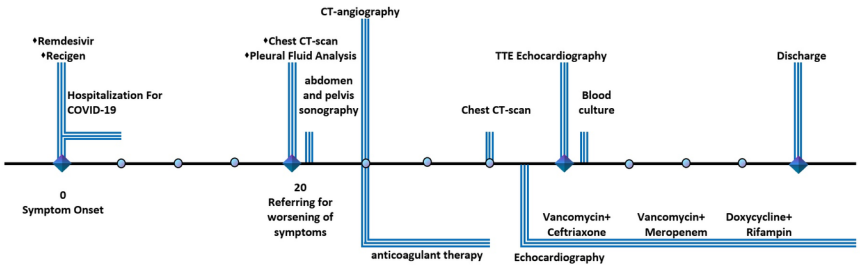

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`Table 1 bartonella.docx` available at https://authorea.com/users/574670/articles/856178-the-importance-of-exposures-in-culture-negative-endocarditis-in-an-iv-drugs-abuser