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Difficult diagnosis infective endocarditis in a pediatric patient: case report

Endocarditis infecciosa de difícil diagnóstico en la edad pediátrica: reporte de caso

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ABSTRACT

Infective endocarditis (IE) remains a diagnostic challenge because its clinical manifestations are nonspecific and mimic other entities. IE has been extensively studied and documented in adults but less so in children. Here we describe a clinical case of IE that is difficult to diagnose. This is a thirteen-year-old male patient who came to the emergency department of the Hospital Infantil Universitario de San José due to fever for one year, predominantly in the afternoon. The patient has a history of corrected myelomeningocele, Arnold Chiari malformation type 1, neurogenic bladder and hydrocephalus and is a user of the ventriculoatrial shunt. On admission, a urinary tract infection by a multidrug-resistant germ was documented, which was initially considered the cause of his fever. Multiple echocardiograms were performed, all without evidence of IE. However, in addition to fever and ventriculoatrial shunt, *Streptococcus mitis* bacteremia and positive rheumatoid factor were documented, establishing a definitive diagnosis of IE according to modified Duke criteria. This case illustrates the importance of maintaining a high suspicion of IE, even in patients with an atypical clinical presentation without specific findings for IE and directing additional studies based on the Duke criteria. This requires knowledge of the typical etiologic microorganisms as well as the findings that constitute the vascular and immunologic phenomena contemplated in the modified Duke criteria.

RESUMEN

La endocarditis infecciosa (EI) continúa siendo un desafío diagnóstico debido a que sus manifestaciones clínicas son inespecíficas y simula otras entidades. La EI ha sido ampliamente estudiada y documentada en adultos, pero no tanto en niños. Aquí se describe un caso clínico de EI de difícil diagnóstico. Se trata de un paciente masculino de 13 años, quien acudió al Servicio de Urgencias del Hospital Infantil Universitario de San José por fiebre durante un año de predominio vespertino. Cuenta con antecedentes de mielomeningocele corregido, malformación de Arnold Chiari tipo 1, vejiga neurogénica e hidrocefalia y es usuario de derivación ventriculoatrial. Al ingreso, se documentó una infección de vías urinarias por un germen multirresistente, la cual inicialmente se consideró la causa de su fiebre. Se realizaron múltiples ecocardiogramas, todos sin evidencia de EI. Sin embargo, además de fiebre y la derivación ventriculoatrial, se documentó bacteriemia por Streptococcus mitis *y factor reumatoide positivo, estableciendo un diagnóstico definitivo de EI según los criterios de Duke modificados. Este caso ilustra la importancia de mantener una alta sospecha de EI, aun en pacientes con una presentación clínica atípica sin hallazgos específicos para EI y dirigir los estudios adicionales con base en los criterios de Duke. Para ello, es necesario conocer cuáles son los microorganismos etiológicos típicos, así como los hallazgos que constituyen los fenómenos vasculares e inmunológicos contemplados en los criterios de Duke modificados.*

INTRODUCTION

Infective endocarditis (IE) is defined as the microbial infection of the endocardium, whether in previously healthy hearts or in susceptible ones with risk factors, like instrumentalization.[1] Nowadays, IE mainly affects patients with congenital cardiopathies, whereas it was previously more common in those with rheumatic cardiomyopathy.[2]

IE is an important disease in the paediatric population, despite having a considerably lower incidence and mortality than adults.[3] The incidence among children with congenital heart disease has been reported to be between 40 and 60 cases per 100,000 such children.[4] Its mortality rates are still significant (5-10% in

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children) despite the progress in the diagnosis and treatment.[5] Here, the case of a male 13-year-old patient with fever is present, multiple comorbidities, positive urine and blood cultures, but no evidence of vegetations on echocardiograms, which led to a delay in the diagnosis.

CASE PRESENTATION

The case involves a 13-year old male patient who presented to the emergency department of the Hospital Infantil Universitario de San José redirected from the neurosurgery outpatient consult due to longstanding fever, predominantly in the evening, of 39-40 ºC, which began after a ventriculoatrial shunt which had been performed year earlier. Relevant medical history includes a correction of myelomeningocele in 2007, type 1 Arnold Chiari malformation, neurogenic bladder for which he receives prophylaxis with trimethoprim-sulfamethoxazole, chronic constipation, flaccid paraparesis and hydrocephalus initially treated with a ventriculoperitoneal shunt, which was subsequently changed to a ventriculoatrial shunt.

On admission, the patient presented no other additional symptoms. On physical examination, he was found to be tachycardic and febrile. A working diagnosis of systemic inflammatory response syndrome of unknown origin was established, for which he was admitted for observation. Initial laboratory testing showed leukocytosis, highly C reactive protein, urine analysis with pyuria, bacteriuria, positive leukocyte esterase and microscopic haematuria. An abdominal echography showed splenomegaly and enlarged kidneys. Because of his medical background, a urinary tract infection (UTI) was diagnosed, and a measurement of procalcitonin was ordered, which came back positive. Urine cultures isolate *E. coli* with an AmpC (serin-betalactamasas) resistance profile, which prompted treatment with ceftriaxone.

The patient had already had a transthoracic echocardiogram (TTE) performed on an outpatient basis, which showed no anomaly. Nevertheless, the study was repeated, documenting free pericardial fluid of 2 mm, with no vegetations or other findings. However, pediatric infectiology considered that regardless of the absence of vegetations infective endocarditis must be suspected and requested additional studies.

On the fifth day of hospitalization, blood cultures isolated *Streptococcus mitis* penicilin sensitive. Additionally, bone scintigraphy that had been performed on an outpatient basis showed nonspecific hyperuptake. Paediatric rheumatology was therefore consulted, who ordered a rheumatoid factor (RF) that was reported positive on day six of hospitalization. With these last findings, and although no vegetations were documented on TTE, the patient was considered to have confirmed infective endocarditis on account of meeting one major criteria (*S. mitis* bacteremia) and three minor criteria (fever > 38 ºC, predisposing heart condition and positive RF) of the modified Duke criteria. Therefore, it was decided to finish seven days of ceftriaxone for the UTI and then initiate antibiotics for the EI with crystalline penicillin for six weeks. As suggested by the pediatric infectious disease consultant since the culprit organism was sensitive to this treatment. The patient response to treatment was favorable with no new febrile peaks, so during the second week of targeted antibiotic therapy the patient was transferred home to complete the remainder of the treatment under a hospitalization-at-home model in charge of healthcare professionals designated by his health insurance company. He subsequently continued to be followed for his multiple comorbidities on an outpatient basis without evidence of recurrence of the IE.

DISCUSSION

In the present clinical case, the diagnosis of IE was made with the modified Duke criteria. According to the literature, it is not frequent to have a patient with all the clinical findings; for instance, Osler nodes and Janeway lesions are found only in 2.7% and 1.6% of patients with IE, respectively.[1] This case was a diagnostic challenge due to the multiple medical comorbidities, which led to the treating physicians towards erroneous diagnoses, like urinary tract infection and renal abscess. A case report was found of a patient with a history of hydrocephalus corrected with VA shunt (ventriculotrial shunt), Arnold

Chiari type 2 malformation, myelomeningocele and glomerulonephritis that after 14 years of the placement of the valve developed IE, which guides to confirm the relevance of such record in this case.[6]

It is crucial to consider IE in the presence of fever of unknown origin, which is found in 90% of all cases associated with risk factors. However, in this instance, despite the fact that pediatric infectology suggested this diagnosis,

Table 1: Modified Duke Infective Endocarditis Criteria.[7]

Mayor criteria	Minor criteria
Blood culture positive for IE A. Typical microorganisms consistent with IE from 2 separate blood cultures: • *Viridans streptococci*, *Streptococcus bovis*, HACEK *group, Staphylococcus aureus*; or • Community-acquired enterococci, in the absence of a primary focus; or B. Microorganisms consistent with IE from persistently positive blood cultures, defined as follows: • At least 2 positive cultures of blood samples drawn 12 h apart; or • All of 3 or a majority of > 4 separate cultures of blood (with first and last sample drawn at least 1 h apart) • Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer > 1: 800 **Evidence of endocardial involvement** A. Echocardiogram positive for IE, defined as follows: • Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • Abscess; or • New partial dehiscence of prosthetic valve B. New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)	• Predisposition, predisposing heart condition or injection drug use • Fever, temperature 38º C • Vascular phenomena — Major arterial emboli — Septic pulmonary infarcts, — Mycotic aneurysm — Intracranial hemorrhage — Conjunctival hemorrhages — Janeway's lesions • Immunologic phenomena — Glomerulonephritis — OSLER'S nodes — ROTH'S spots — Rheumatoid factor • Microbiological evidence: — Positive blood culture but does not meet a major criterion as noted above — Serological evidence of active infection with organism consistent with IE
Definite infective endocarditis • 2 major criteria or • 1 major criterion and 3 minor criteria or • 5 minor criteria **Possible infective endocarditis** • 1 major criterion and 1 minor criterion or • 3 minor criteria **Rejected** 1. Firm alternate diagnosis explaining evidence of infective endocarditis; or 2. Resolution of infective endocarditis syndrome with antibiotic therapy for ≤ 4 days 3. No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤ 4 days 4. Does not meet criteria for possible infective endocarditis, as above	

IE = infective endocarditis; HACEK = Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella; IgG = immunoglobulin G.

cardiology did not consider it due to the absence of vegetations on cardiac image and by distractors that suggested other sources of infection. The placement of the AVD a year ago and the subsequent onset of fever was not taken into proper consideration. These findings pointed to IE from the beginning and should not have been disregarded despite a negative echocardiogram.

According to the reviewed literature, echocardiograms should always be interpreted in the light of clinical findings and blood cultures. Therefore, the presence of a normal image does not rule out the existence of IE, as sensitivity is 75% and specificity is 90%.[8] It is recommended that if clinical suspicion is high normal TTE should be followed up with a transesophageal echocardiogram (TEE), which has a sensitivity of 90%. Despite, in childhood TEE is rarely needed, it can help in cases such as: aortic root abscess, prosthetic valves, chest wall deformity and obesity. Unfortunately, this test was not performed because the patient's health insurance did not authorize it. In the absence of images showing myocardial compromise, the presence of other findings that suggest heart disease, such as clinical signs or symptoms of heart failure or elevations in pro-BNP levels, should increase the index of suspicion. The patient in this case did not present such clinical findings and the pro-BNP (brain natriuretic peptide) was not documented because this lab test was authorized by his health insurance. However, not all patients with IE develop heart failure or may do so only late in the disease course. Therefore, the absence of such findings does not rule out IE. Nevertheless, in the absence of direct evidence of myocardial involvement, as in this case, it is necessary to differentiate simple bacteremia from IE. The modified Duke criteria are an invaluable tool in this sense as they allow us to make this difficult differential diagnosis. Bacteremia with a typical organism meets a major criteria, but is not by itself sufficient to establish a diagnosis of definitive IE. Instead, at least one other major or three minor criteria must also be met. (The modified Duke criteria even indicate that definitive IE should be diagnosed if five minor criteria are present, even in the absence of any major criteria.) As described above, this patient met one major criteria and three minor criteria, so a diagnosis of definitive IE rather than simple bacteremia is justified according to the modified Duke criteria *(Table 1)*.

Regarding treatment, IE, like many diseases in pediatrics, there is insufficient evidence to allow adequate comparison between alternative therapies. Treatment regimens are therefore chosen on the basis of regimens used for the adult population, with the first line of empirical treatment being ampicillin/sulbactam and aminoglycosides according to American Heart Association (AHA) guidelines.[4] Comparing AHA 2015 guidelines and European Society of Cardiology (ESC) guidelines, it can be seen that both of them recommend the use of bactericides over bacteriostatics.[3,9] Regarding treatment, AHA recommends IV medication for a treatment period of four-eight weeks.[10] As for the case, the change of antibiotic was made due to the resolution of the UTI and the sensitivity shown by the cultures.

CONCLUSIONS

A normal echocardiogram does not exclude the diagnosis of endocarditis, and a repeat echocardiogram may be indicated.

In the clinical scenario, there may be multiple antecedents together with non-specific clinical manifestations that may lead to other etiologies and to an erroneous diagnosis, leading to a delay in the appropriate treatment, so management should always be multidisciplinary.

Transesophageal echocardiography is a very useful diagnostic tool in this type of case in which we have negative transthoracic echocardiograms.

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