SN Comprehensive Clinical Medicine
https://doi.org/10.1007/s42399-021-00955-8

IMAGING

^{18}F-Fluorodeoxyglucose Positron Emission Tomography: a Useful Tool for the Diagnosis of Endocarditis in a Boy with Congenital Heart Disease: a Case Report

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Accepted: 7 May 2021

Abstract

Actinobacillus actinomycetemcomitans is a Gram-negative coccobacillus responsible for blood culture-negative endocarditis. This type of endocarditis is difficult to diagnose because of its insidious evolution and variability of symptoms. Moreover, valvular vegetation may be challenging to detect by echocardiography, especially in children with congenital heart disease. ^{18}F-fluorodeoxyglucose positron emission tomography is frequently used as an additional diagnostic tool for infectious endocarditis in adult patients, and has proved efficient, especially for prosthetic valves. However, its value has been rarely described for the diagnosis of infectious endocarditis in children with congenital heart disease. The authors report the case of an 11-year-old boy with congenital aortic stenosis, who developed severe anemia, thrombocytopenia, hepatosplenomegaly, acute kidney injury, and biological signs of inflammation, with only very mild fever. Renal biopsy revealed the presence of crescentic glomerulonephritis. Transthoracic and transoesophageal echocardiography did not show any vegetation. An ^{18}F-fluorodeoxyglucose positron emission tomography was performed and revealed abnormal ^{18}F-FDG uptake in the area of the aortic valve, supporting the hypothesis of infectious endocarditis. The patient underwent cardiac surgery for the reparation of the aortic stenosis and calcified vegetation was found and resected from the aortic valve. One blood culture yielded *Actinobacillus actinomycetemcomitans* after 20 days. However, the PCR for the 16S rRNA gene on the resected vegetation was negative. He was treated with 4 weeks of parenteral antibiotics. Follow-up showed the resolution of the clinical and biological abnormalities within a few days. Blood culture-negative endocarditis should be considered in a child with multiorgan manifestations, such as thrombocytopenia, hepatosplenomegaly, and glomerulonephritis. Because echocardiography may not show valvular vegetation, especially in children with pre-existing valvular heart disease, ^{18}F-fluorodeoxyglucose positron emission tomography can be useful to confirm the diagnosis of endocarditis in these patients.

Keywords *Actinobacillus actinomycetemcomitans* · Endocarditis · Glomerulonephritis · ^{18}F-fluorodeoxyglucose positron emission tomography · Case report

Introduction

Actinobacillus actinomycetemcomitans is a Gram-negative coccobacillus responsible for blood culture-negative endocarditis. This type of endocarditis is difficult to diagnose because of its insidious evolution and variability of symptoms. Moreover, valvular vegetation may be challenging to detect by echocardiography, especially in children with congenital heart disease. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT) is frequently used as an additional diagnostic tool for infectious endocarditis in adult patients, and has proved efficient, especially for prosthetic valves. However, its value has been rarely described for the diagnosis of infectious endocarditis in children with congenital heart disease. The case described below is an example of an infectious endocarditis diagnosed by ^{18}F-FDG PET/CT in a child with congenital heart disease.

This article is part of the Topical Collection on *Imaging*

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Published online: 26 May 2021

Case Presentation

We present the case of an 11-year-old boy, transferred from Algeria for the surgical management of bicuspid aortic valve with severe aortic stenosis. The patient has no other medical or surgical history. He arrived with a 2-month history of intermittent fever, weight loss, pallor, and microscopic hematuria. On admission, physical examination identified a grade IV/VI systolic ejection murmur, and splenomegaly. Initial laboratory evaluation only showed isolated severe anemia (hemoglobin 6.1 g/dl), and no hyperleukocytosis or other signs of inflammation. Besides the aortic stenosis, the transthoracic echography (TTE) and the cardiac catheterization revealed a fistula between the Valsalva sinus and the coronary sinus (Fig. 1), but no valvular vegetation. Within a few days, the patient developed severe thrombocytopenia (minimum of 34,000/mm^3 platelets) and progressive acute kidney injury (maximum of 2,4 mg/dl of creatinine), with biological signs of inflammation (C-reactive protein of maximum 159 mg/l, ferritin of maximum 945 µg/l, and fibrinogen of maximum 945 mg/dl). Clinically, within a week, the splenomegaly and the hematuria gradually got worse, and enlarged liver was found. Fever was exceptional and rectal temperature did not exceed 38.1°C. Multiple investigations were done: Bone marrow aspiration was normal, ruling out hematologic malignancies; serology for HIV was negative; quantiferon and intradermoreaction showed no sign of tuberculosis; and auto-immune antibodies were negative, including normal C3 level. A renal biopsy was performed and revealed crescentic glomerulonephritis. Multiple serologic tests including for *Coxiella burnetii*, *Bartonella*, *Brucella*, and *Histoplasma capsulatum* were negative. No virus or bacteria was detected by polymerase chain reaction (PCR) on blood samples. Eight blood samples were taken, but the blood culture was still in process. At this point, there were 3 minor criteria of the modified Duke criteria: a predisposing heart condition, a temperature of > 38°C, and a glomerulonephritis. Because the diagnosis of infective endocarditis (IE) was considered, TTE was repeated and transoesophageal echography (TOE) performed, but neither imaging procedure showed any vegetation. An ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT) was performed, but was inconclusive because of inadequate cardiac preparation. The patient was not receiving any antibiotics at that point. Because the symptoms were getting worse, another ^{18}F-FDG PET/CT with optimal cardiac preparation (low carbohydrate–fat allowed diet) was conducted, 6 weeks after the TOE, and 2 weeks after the last TTE and the first PET/CT, and showed abnormal ^{18}F-FDG uptake in the area of the aortic valve (Fig. 2), supporting the hypothesis of endocarditis. Further testing including brain MRI revealed the presence of cerebral microbleeds and no septic embolus.

Surgical management of the aortic stenosis was decided after a diagnosis of probable endocarditis on the basis of the bicytopenia, glomerulonephritis, fever, and abnormal ^{18}F-FDG uptake on the aortic valve, and before any antibiotherapy was started. The surgery consisted of aortic valve repair and closure of the fistula between the Valsalva sinus and the coronary sinus, probably of congenital origin. A calcified vegetation was found on the aortic valve and resected (Fig. 3). Histopathology of the vegetation showed a lymphohistiocytic infiltration rich in neutrophils compatible with IE. Surprisingly, no bacteria was detected by PCR 16-S on the resected vegetation. However, two separate cultures of the vegetation revealed the presence of *Staphylococcus aureus* (SA) in one, and *Streptococcus salivarius* in the other. Because of this discordant result, these two bacteria were considered contaminants. Finally, one of the blood cultures obtained before surgery was positive for *Actinobacillus actinomycetemcomitans* (AA) after 20 days.

The patient received intravenous ceftriaxone for 4 consecutive weeks after surgery (3 g/day). Corticosteroids (2 mg/kg/day) were also started 4 days after surgery, and administered for 10 days, to slow the progression of the crescentic

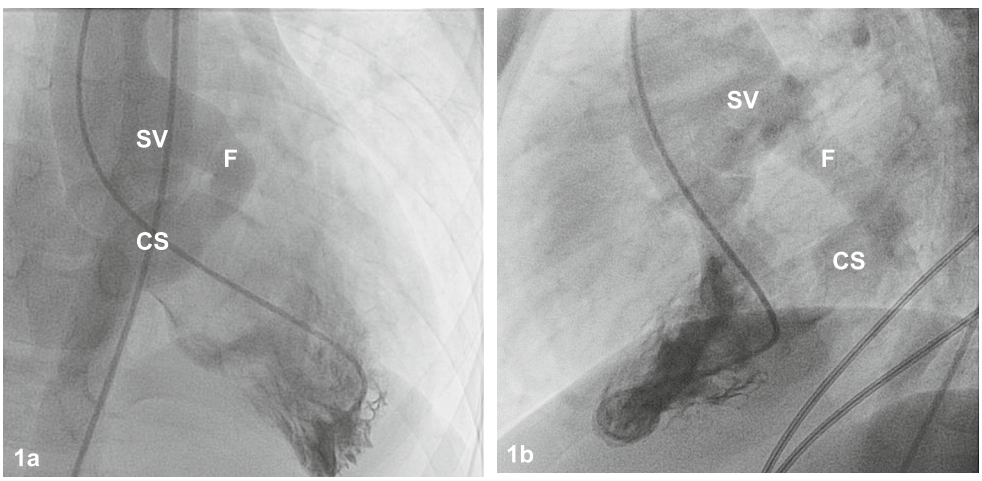

Fig. 1 Left ventriculography with lateral anterior oblique 13° and cranial 16° view (**a**) and lateral anterior oblique 88° and caudal 2° view (**b**), showing the fistula (F) between the Valsalva sinus (VS) and the coronary sinus (CS)

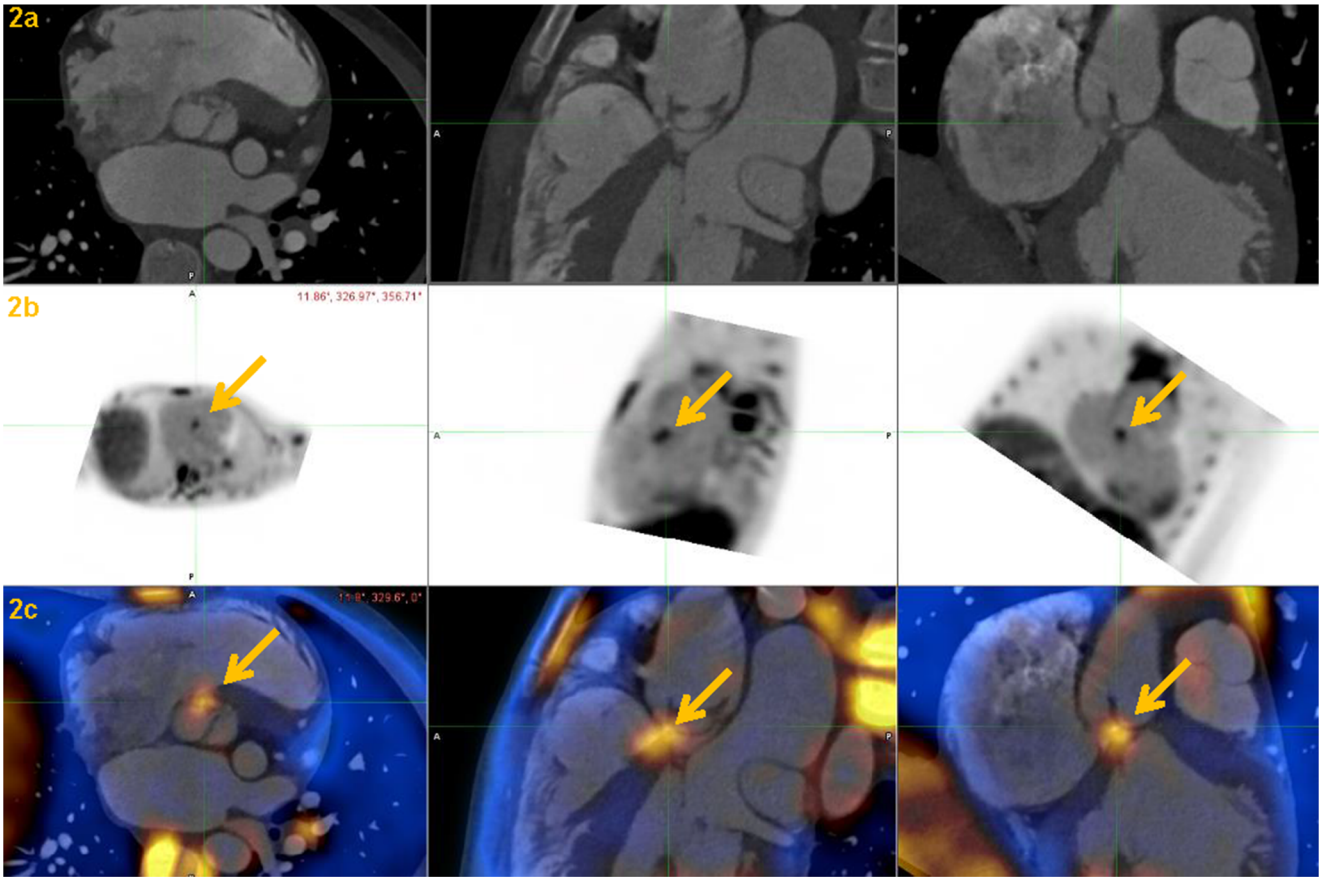

Fig. 2 Co-registered ^{18}F-FDG PET-angioCT images showing the abnormal tracer uptake on the aortic valve (right coronary cuspide's root [arrows]). **a** Preoperative CT angiography. **b** ^{18}F-FDG part of the PET-CT. **c** Co-registered **a** and **b** images

glomerulonephritis. Although endocarditis caused by SA was unlikely given the clinical picture and the discordant results of the valve cultures, doxycycline (120 mg/day) was added to ceftriaxone to treat SA, until we were sure the PCR-16S was negative. On follow-up, inflammation, bicytopenia, and renal injury resolved in a few days, as well as the hepatosplenomegaly and macroscopic hematuria. There were no complications or adverse events of the surgical or medical treatment, and the medications were well tolerated. Dental examination was performed, and two dental caries were treated.

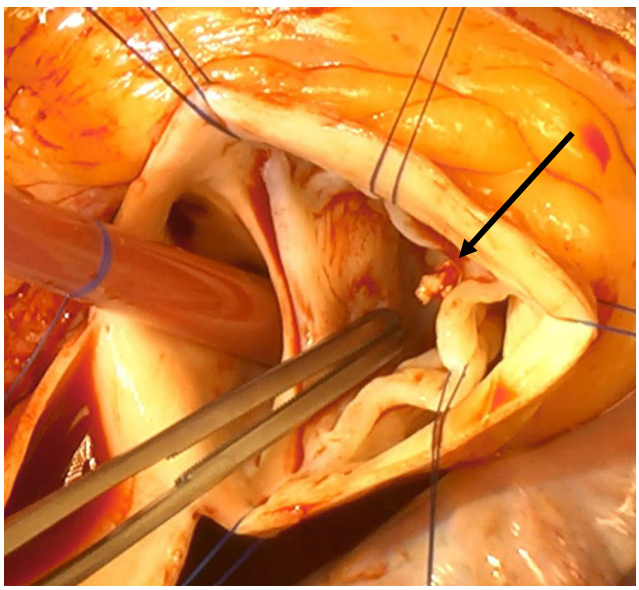

Fig. 3 Peroperative view: calcified vegetation (arrow) on the aortic valve

Discussion

Actinobacillus actinomycetemcomitans (AA) is a Gram-negative coccobacillus categorized as a member of the HACEK group (*Haemophilus parainfluenza*, *aphrophilus*, *paraphrophilus*, and *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella kingae*) [1–5]. HACEK organisms are grouped together as fastidious, Gram-negative bacteria of the oral flora that require growth factors and carbon dioxide for isolation and culture. They are the most common cause of pediatric Gram-negative endocarditis [1]. Among reported cases of AA endocarditis in adults and children, the aortic and mitral valves were most often involved [2].

Symptoms of endocarditis caused by AA develop insidiously [3]. Fever is mostly present but intermittent. The subacute or chronic onset of the disease compromises early diagnosis. Other manifestations such as anemia, thrombocytopenia, hepatosplenomegaly, or glomerulonephritis may also confound the diagnosis of endocarditis. In 2004, Paturel et al. [3] reviewed pediatric and adult cases of AA endocarditis, among which 6.6% had hepatosplenomegaly, 88% mild or severe anemia, 69.4% microscopic hematuria, and 22.8% elevated creatinine levels. However, rapidly progressive glomerulonephritis (RPGN) with macroscopic hematuria, proteinuria, and acute renal injury has been rarely described with AA endocarditis [6]. The microvascular/immunological response caused by HACEK endocarditis may explain why the patients develop glomerulonephritis, as well as cerebral microbleeds, more frequently than in non-HACEK endocarditis [4]. In our patient, both RPGN and cerebral microbleeds were present.

For a decade, ^{18}F-FDG PET/CT has become an important adjunctive diagnostic tool for IE in adult patients, especially for prosthetic valves [7–13]. Its use has been integrated in the European Society of Cardiology guidelines for the management of IE [7, 8]. It has also shown a prognostic value, predicting major cardiac events in prosthetic valves and new embolic events within the first year following the IE [9]. ^{18}F-FDG is a glucose analog radiotracer that accumulates in regions of high metabolism, such as infected regions with inflammatory cells (macrophages, neutrophils, and lymphocytes) that overexpress the glucose transporters GLUT1 and GLUT4. The study by Pizzi et al. published in 2015 in whom 92 patients with prosthetic valve or cardiac device were prospectively included showed that the use of ^{18}F-FDG PET/CT improves the diagnosis of IE in these patients, with a sensitivity and specificity of 90.7% and 89.5% for Duke criteria + ^{18}F-FDG PET/CT, compared to 52% and 94.7% for Duke criteria only [10]. However, in patients with IE of native valves, the sensitivity of ^{18}F-FDG PET/CT is markedly lower compared with prosthetic valves [7–13]. In 2019, a large prospective study of 303 suspected IE, 188 in patients with prosthetic valves and 115 with native valves, found sensitivity and specificity of 93% and 90% for Duke criteria + ^{18}F-FDG PET/CT in patients with prosthetic valves vs. 22% and 100% for patients with native valves. This may be explained by low level of metabolism, vegetation size, heart movement, and background tracer uptake [7]. The case of our patient is an example of native valve IE in a pediatric patient with congenital heart disease, diagnosed by ^{18}F-FDG PET/CT, while TTE and TOE were negative. This not only illustrates the limitations of echocardiography in diagnosing IE in children with congenital heart disease, but also highlights the value of ^{18}F-FDG PET/CT in such patients. In our patient, the remodeled shape of the bicuspid aortic valve was probably an advantage for the diagnosis by PET/CT, because it is less mobile than a healthy native valve, which makes it easier to observe by PET/CT. Thus, even if diagnostic sensitivity of ^{18}F-FDG PET/CT is lower than in prosthetic valve, it could be interesting to use it in native valve if TTE and TOE are negative, especially in congenital heart disease. Moreover, an adequate cardiac preparation (low carbohydrate–fat allowed diet) is crucial before performing the PET/CT; otherwise, it may lead to inconclusive results, which happened with the first PET/CT of our patient. This case report demonstrated that ^{18}F-FDG PET/CT assessment, in addition to the modified Duke criteria, could improve the diagnostic value in pediatric congenital heart disease.

HACEK endocarditis should be considered in suspected IE with sterile blood culture. Because HACEK microorganisms are slow-growing, prolonged incubation of blood culture is necessary to identify the pathogen [14]. The other fastidious slow-growing bacteria responsible for blood culture-negative endocarditis are essentially *Bartonella* sp., *Coxiella burnetii*, *Legionella pneumophila*, and *Mycoplasma pneumoniae* for which serological testing can be done [15]. A PCR should also be immediately performed to help detect the causative pathogen and determine an appropriate management [4]. Furthermore, the value of heart valve culture is low, in contrast with 16S-rDNA sequencing of valve material [16]. In 2019, Halavaara et al. published a study in which only 22% of patients with infective endocarditis had a positive valve culture, whereas 85% of patients had positive blood culture and 74% a positive 16S rRNA PCR [17]. Among the patients with positive valve cultures, two of them had different microbiological findings in the blood and in the valve, as in our patient. Moreover, culture of resected heart valves may also be positive in patients without IE, as observed by Munoz et al. in a study published in 2008: 28.4% of cultures were positive in non-infective endocarditis cases [18]. This is the result of perioperative or laboratory contamination, and the usual microorganisms found in those cultures are coagulase-negative staphylococci, Viridans group *Streptococcus* species, *Enterococcus* species, and *S. aureus*. In this study, among the patients with IE, only 39.4% of the cultures were positive, concluding that even in patients with IE, the results of valve culture should be interpreted with caution. For these reasons, the two different bacteria found in the culture of the resected vegetation in our patient were considered contaminants. In the case of our patient, universal PCR for the 16S rDNA gene was performed on the resected vegetation, but did not help detecting the presence of AA, though several studies show that causative pathogens are identified by PCR for the 16S rDNA gene on valve material in 75% of blood culture-negative endocarditis cases [15, 19].

AA is described as highly sensitive to antibiotics [2], providing a good prognosis of AA endocarditis when treated. Ceftriaxone is the recommended antibiotic for HACEK and the duration of treatment for a native valve should be of 4-6

weeks according to the American Heart Association guidelines [20], and has shown very good activity against AA [21].

Conclusion

Actinobacillus actinomycetemcomitans is a microorganism responsible for blood culture-negative endocarditis. This type of endocarditis is insidious, and the variability of symptoms may confound the diagnosis. TEE and TOE may not show any sign of valvular vegetation, especially in children with pre-existing valvular heart disease, and therefore, cardiac ^{18}F-FDG PET/CT can be very useful to confirm the diagnosis of endocarditis, with strict adherence to the preparation diet. Repeated blood cultures with prolonged incubation are an important diagnostic tool, but because they do not always yield the pathogen, PCR on the blood and 16-S rRNA PCR on the resected heart tissue should also be performed. However, the value of heart valve culture is low, partly because it can be contaminated during surgery. Finally, when treated surgically or with antibiotics, blood culture-negative endocarditis has a good prognosis, with a good prognosis of extra-cardiac manifestations.

Author Contribution Elise Balligand, Cielo Rojas, Celine Themelin, Laetitia Vanhoutte, and Christophe Vo contributed to the daily management of the patient in the pediatric cardiology ward. Dimitri Van Der Linden gave his advice as expert in pediatric infectious diseases, and Nathalie Godefroid gave hers as expert in pediatric nephrology. Véronique Roelants performed and interpreted the ^{18}F-FDG PET/CT, Alain Poncelet performed the cardiac surgery, and Pamela Baldin the histopathologic analysis of the cardiac tissue.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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