

Integration of ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography in Diagnostic Algorithm of Prosthetic Valve Endocarditis: A Case Report and Review of Literature

Abstract

Prosthetic valve endocarditis (PVE) is a sinister complication, with high morbidity and mortality. Diagnosis is conventionally based on modified Duke Criteria. ¹⁸F-Fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography-computed tomography (PET-CT) has shown high accuracy in diagnosing PVE. Positive ¹⁸F-FDG uptake in prosthetic valves on PET-CT is now considered major criteria for diagnosis of PVE. We share our experience of ¹⁸F-FDG PET-CT imaging as a problem solving tool in a case of suspected PVE and review the relevant literature.

Keywords: ¹⁸F-fluorodeoxyglucose, *Candida*, endocarditis, positron emission tomography-computed tomography, prosthetic valve

Introduction

Prosthetic valve endocarditis (PVE) is a potentially life-threatening complication with an annual incidence of 0.3%–1.2% and accounting for about 25% of all cases of infective endocarditis (IE).^[1] Aortic valve is most commonly involved (66.5%), followed by mitral (40.7%), tricuspid (2.9%), and multiple valves (7.2%).^[2] PVE is usually bacterial, with fungal infection accounting for only 4% cases.^[3] ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography-computed tomography (PET-CT) has shown utility in diagnosis of IE, especially PVE.^[4] Positive ¹⁸F-FDG PET-CT has been inducted as a major criterion for IE diagnosis in the European Society of Cardiology (ESC) guidelines.^[5] We present a case of fungal PVE, where ¹⁸F-FDG PET-CT played an important role in management and review the available literature in this regard.

Case Report

A 58-year-old man presented at our hospital with palpitation and chest discomfort. There was no fever. He had a history of mitral valve replacement with a bioprosthetic valve, 9 years back. He was diabetic and hypertensive, relatively well controlled with oral medications. Blood tests showed

normal total leukocyte count (5400/ml, normal: 4000–10,000), raised C-reactive protein (1.7 mg/L, normal <0.5), raised serum procalcitonin (1.3 ng/ml, normal <0.5), and elevated brain natriuretic peptide (845.7 pg/ml, normal <100). Electrocardiogram showed atrial fibrillation. Transthoracic echocardiography (TTE) showed post mitral valve replacement status, with some suspicion of vegetations, mild pulmonary arterial hypertension, and normal cardiac function (ejection fraction 60%). Transesophageal echocardiography (TEE) was then performed which showed multiple mobile masses attached to the bioprosthetic mitral valve with out-of-phase motion and severe mitral stenosis. With suspicion of IE, multiple aerobic and anaerobic blood cultures were sent, all were negative. Based on Duke Criteria,^[6] a diagnosis of possible PVE was made (one major and one minor criteria). The cardiologist then advised cardiac ¹⁸F-FDG PET-CT for further evaluation. The patient was prepared with a combination of 24 h of low carbohydrate and fat rich diet, 12 h fasting and intravenous unfractionated heparin (50 IU/kg, 15 min before ¹⁸F-FDG), to suppress physiological myocardial ¹⁸F-FDG uptake.^[7] Cardiac PET-CT [Figure 1, arrows] showed a focal area of increased ¹⁸F-FDG uptake in

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Received: 08-08-2020

Revised: 14-08-2020

Accepted: 17-08-2020

Published: 21-06-2021

Access this article online

Website: www.ijnm.in

DOI: 10.4103/ijnm.IJNM_184_20

Quick Response Code:



How to cite this article: Sharma P, Banerjee S. Integration of ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography in diagnostic algorithm of prosthetic valve endocarditis: A case report and review of literature. Indian J Nucl Med 2021;36:173-8.

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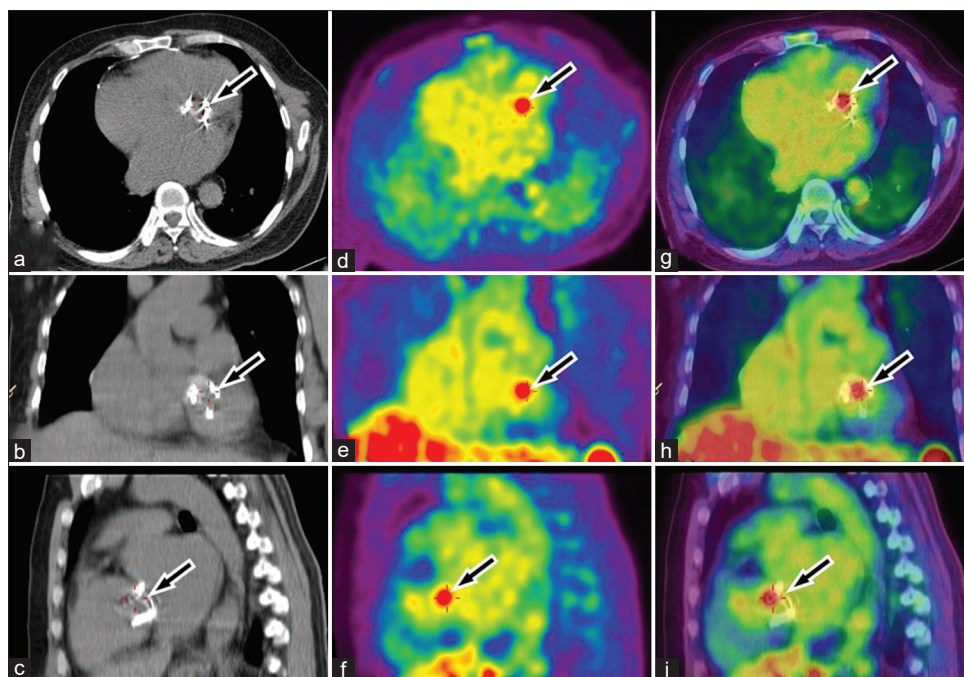


Figure 1: Transaxial (a), coronal (b) and sagittal (c) noncontrast computed tomography images show the mitral prosthetic valve (arrow). On transaxial (d), coronal (e) and sagittal (f) positron emission tomography, and transaxial (g), coronal (h), and sagittal (i) fused positron emission tomography-computed tomography images, focal increased ^{18}F -fluorodeoxyglucose uptake is seen in the prosthetic valve (arrow, SUV_{max} 5.3), suggestive of prosthetic valve endocarditis. Post removal culture from the prosthetic valve showed growth of *Candida albicans*

the region of the prosthetic valve (SUV_{max} 5.3, blood pool 2.0). No periannular uptake was seen. The uptake was not visually different on nonattenuation corrected PET images. As the patient did not have any features of septic embolism, whole body imaging was not performed. Based on ^{18}F -FDG PET-CT findings and ESC 2015 guidelines,^[5] a diagnosis of PVE was made. The patient underwent a redo mitral valve replacement with mosaic porcine bioprosthesis. Culture of the removed prosthetic valve showed growth of *Candida albicans*, sensitive to amphotericin and fluconazole. The patient was given 2 weeks of intravenous amphotericin B and then discharged in stable condition on oral fluconazole. He was doing fine with a 3 years' follow-up.

Discussion

PVE is a dreaded complication of valve replacement. Although data are conflicting, risk of PVE is considered higher for bioprosthetic valves compared to mechanical valves.^[8] PVE is classified into two temporal groups, early PVE, occurring within 1 year (usually 2 months) of replacement, usually caused by nosocomial microbes such as *Staphylococci*, Gram-negative bacilli, and *Candida*, and late PVE, occurring beyond 1 year, usually caused by *Streptococci*, *Staphylococcus aureus*, *Enterococci*, and *Fastidious* Gram-negative bacteria.^[3] The former is associated with infection of surrounding tissue, causing perivalvular abscess and paravalvular leak. The latter is associated with formation of platelet-fibrin thrombi on the valve leaflet, later seeded with microbes.^[9] Therefore, differentiation of bland thrombi from infected vegetation

is important from a clinical perspective, even more so, if classical pictures of IE are absent and blood cultures are negative, as was in the present case.^[10] PVE caused by *Candida* is more sinister, has subacute presentation, large vegetations, poor yields from blood culture and needs aggressive management with redo valve replacement and antifungals.^[11] The same management strategy was followed in the present case.

A positive blood culture along with suggestive imaging, forms the basis for PVE diagnosis.^[1] Blood culture is positive in a large proportion of PVE patients, but can be negative in early disease, after antibiotic therapy, or if caused by fastidious bacteria and fungus, as in the present case. The imaging modalities for PVE include TTE, TEE, CT, and PET-CT.^[3] While TTE is safe, cheap and widely available, it is dependent on the operator and imaging window, and has overall poor sensitivity, but high specificity. TEE is also relatively safe and widely available, has high sensitivity and specificity, and is usually the preferred imaging for PVE. Unfortunately, it also suffers from the drawbacks of operator and imaging window dependence. Multislice CT is moderately sensitive and specific for PVE, and allows assessment of coronary arteries in the same setting, but is costlier and also entails radiation exposure, unlike TTE or TEE. It can also show artefacts because of the valve.

^{18}F -FDG PET-CT is an important supplementary diagnostic method in cases of PVE.^[12] A detailed overview of available literature pertaining to the role of ^{18}F -FDG PET-CT in PVE

Table 1: Literature review of the role of ¹⁸F-Fluorodeoxyglucose positron emission tomography-computed tomography in prosthetic valve endocarditis

Author	Year	Study design	Number (PVE/total)	¹⁸ F-FDG PET-CT protocol	¹⁸ F-FDG PET-CT analysis	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Remarks
Saby <i>et al.</i> ^[13]	2013	Single center, prospective	72/72	High fat, carbohydrate restricted diet, long fasting	Visual analysis AC and NAC, SUV max at PV and blood pool in right atrium, SUV ratio of PV/ blood pool	Modified Duke criteria, expert team review, 3-month follow-up	62% (47-75)	80% (56-94)	-
Camargo <i>et al.</i> ^[14]	2013	Retrospective, single center	29/29	-	-	Modified Duke criteria	83% (59-96)	73% (39-94)	-
Rouzet <i>et al.</i> ^[15]	2014	Single-center, retrospective	39/39	High fat, carbohydrate restricted diet, long fasting	Visual analysis AC and NAC, SUV mean at PV and blood pool in right atrium, PV-background ratio=SUV mean PV/ blood pool	Expert team review based on clinical and echocardiographic data, 3-month follow-up	93%	71%	Leukocyte scintigraphy less sensitive more specific
Riccardi <i>et al.</i> ^[16]	2014	Retrospective, single center	27/27	High fat, carbohydrate restricted diet, fasting	-	Modified Duke criteria	64% (43-82)	100% (16-100)	-
Chirillo <i>et al.</i> ^[17]	2014	Single center	19/45	-	-	Modified Duke criteria, 6-month follow-up	87% (69-96)	67% (38-88)	Increased sensitivity of Duke criteria
Pizzi <i>et al.</i> ^[18]	2015	Single center, prospective	92/92	Long fasting and heparin, gated cardiac PET with CT angiography	Visual analysis AC and NAC, SUV _{max} at PV and blood pool, SUV ratio of PV/blood pool	Expert team review based on echocardiogram, culture and clinical data	89% (77-96)	84% (69-94)	Also included CIED
Jiménez-Ballvé <i>et al.</i> ^[19]	2016	Single center, prospective	41/41	High fat, carbohydrate restricted diet, fasting and heparin	Visual analysis AC and NAC, SUV _{max} at PV, liver blood pool, 5 point scale	Culture/ histopathology of surgical specimen or expert team opinion with 4-month follow-up	100% (86-100)	28% (10-53)	-
Fagman <i>et al.</i> ^[20]	2016	Single center, retrospective	11/11	Prolonged fasting	Visual analysis AC and NAC, SUV _{max} at PV and blood pool, SUV ratio PV/ blood pool	Modified Duke Criteria, expert team review	67% (30-93)	100% (16-100)	-
Granados <i>et al.</i> ^[21]	2016	Retrospective, single center	80/80	Prolonged fasting, heparin	Visual analysis AC and NAC, SUV max at PV, SUV mean of blood pool (SVC/ liver), SUV ratio PV/blood pool	Modified Duke Criteria by expert team, 6- month follow-up	61% (36-83)	94% (80-99)	-

Contd...

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Author	Year	Study design	Number (PVE/total)	¹⁸ F-FDG PET-CT protocol	¹⁸ F-FDG PET-CT analysis	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	Remarks
Zhang-Yin <i>et al.</i> ^[22]	2016	Single center, retrospective	23/35	High fat, carbohydrate restricted diet	Visual analysis AC and NAC, SUV _{max} at PV and blood pool in right atrium, SUV ratio PV/blood pool	Dukes criteria, expert team review	92%	77%	Mixed population of prosthetic valve and other devices
Kokalova <i>et al.</i> ^[23]	2017	Single-center, retrospective	13/13	High fat, carbohydrate restricted diet, fasting	Visual analysis AC and NAC	Histopathology or microbiology	90.9%	100%	-
Salomäki <i>et al.</i> ^[24]	2017	Single-center, prospective	16/23	High fat, carbohydrate restricted diet, long fasting	Visual analysis AC and NAC, SUV _{max} at PV	Expert committee review	-	-	Extra-cardiac foci in 58%
Swart <i>et al.</i> ^[25]	2018	Multicenter, prospective	160/160	High fat, carbohydrate restricted diet, fasting, heparin	Visual analysis AC and NAC, SUV _{max} of PV, SUV ratio with blood pool	Expert committee review	91%	95%	
El-Dalati <i>et al.</i> ^[26]	2019	Single-center, retrospective	8/14	High fat, carbohydrate restricted diet, fasting, heparin	Visual analysis AC and NAC, SUV _{max} PV and blood pool	Intraoperative findings	-	-	-
Philip <i>et al.</i> ^[27]	2020	Multicenter, prospective	115/115	High fat, carbohydrate restricted diet, long fasting	Visual analysis AC and NAC	Expert team review	73.6%(63.3-82.0)	75% (53.3-90.2)	Improved accuracy of Dukes criteria
de Camargo <i>et al.</i> ^[28]	2020	Single-center, prospective	188/303	High fat, carbohydrate restricted diet, fasting	Visual analysis AC and NAC, SUV _{max} at PV	Expert team review	91%	94%	Improved accuracy of Duke criteria
Gomes <i>et al.</i> ^[29]	2020	Single-center, prospective	37/176	High fat, carbohydrate restricted diet, fasting	Visual, scoring based on PV, liver and blood pool	Expert review	83%	86%	-

PVE: Prosthetic valve endocarditis, CI: Confidence interval, AC: Attenuation corrected images, NAC: Non-attenuation corrected images, SUV: Standardized uptake value, PV: Prosthetic valve, CIED: Cardiovascular Implantable Electronic Device, ¹⁸F-FDG: ¹⁸F-Fluorodeoxyglucose, PET-CT: Positron emission tomography-computed tomography

is presented in Table 1.^[13-29] A recent meta-analysis by Wang *et al.*^[30] showed a pooled sensitivity of 80.5% (95% confidence interval [CI] 74.1%–86.0%) and specificity of 73.1% (95% CI 63.8–81.2%) in PVE. In addition, if the whole body PET-CT is performed it can pick up additional extra-cardiac septic foci in about 17% of patients.^[31,32] Abnormal focal ¹⁸F-FDG uptake at the site of prosthetic valve (implanted more than 3 months before) is now a major criterion, which significantly increases the sensitivity of the modified Duke Criteria from 70% to 97% without changing the specificity.^[13] It is especially useful in the

category of “possible IE.” While semi-quantitative analyses have been performed by many authors, visual analysis of PET-CT is as accurate and should be compared with the cardiac blood pool, traditionally in the right atrium. Care must be taken for adequate preparation of patients with different combinations of fasting, carbohydrate restricted fat rich diet and heparin, so as to optimally suppress the physiological myocardial ¹⁸F-FDG uptake, which can interfere with image interpretation in PVE. Familiarity with patterns of ¹⁸F-FDG uptake in normal prosthetic valves is also essential.^[33] Normal uptake is usually mild

Table 2: List of radiopharmaceuticals for infection imaging

¹⁸ F-FDG*
⁶⁷ Ga-Citrate
Labeled leukocyte
<i>In-vitro labeling*</i>
^{99m} Tc-HMPAO*
¹¹¹ In-Oxine*
¹⁸ F-FDG
<i>In vivo labeling</i>
^{99m} Tc-Sulesomab (antibody fragment)
^{99m} Tc-Fanolesomab (whole antibody)
Labeled antibiotics
^{99m} Tc-Ciprofloxacin
Labeled antimicrobial peptide
^{99m} Tc-Ubiquicidin

*Denotes commonly used tracers. FDG: Fluorodeoxyglucose, HMPAO: Hexamethylene-propylene amine oxime

to moderate, homogeneous, periannular, and less marked in non-attenuation corrected PET images. Intense normal uptake can be seen around recently implanted valves, up to 3 months. The barriers to routine use of ¹⁸F-FDG PET-CT in PVE are its limited availability, higher cost and risk of radiation exposure. Apart from ¹⁸F-FDG, a wide array of radiopharmaceuticals have been used for infection imaging [Table 2].^[34] Of particular interest in PVE is leukocyte imaging.^[15] The advantages of leukocyte imaging over ¹⁸F-FDG PET-CT are its high specificity for the diagnosis of infective foci and lack of confounding physiological uptake in myocardium. On the negative side radiolabeling of leukocytes is a laborious and time consuming process, carries risk of handling blood products, and total imaging time is very long. In addition, the low spatial resolution of gamma imaging compared to PET is also a drawback reducing sensitivity, though that can be overcome using ¹⁸F-FDG labeled leukocytes.

In conclusion, ¹⁸F-FDG PET-CT shows high accuracy for diagnosis of PVE and should be integrated in the diagnostic algorithms. It is especially useful in cases where other tests are equivocal and those with diagnosis of “possible IE” based on Duke Criteria.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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