Detection of extra-cardiac hypermetabolic foci by [^{18}F]FDG PET/CT in case of infective endocarditis and post antibiotic therapy response assessment

Case Report

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ABSTRACT

The diagnosis of prosthetic valve endocarditis continues to present a diagnostic challenge, due to the lower sensitivity of the modified Duke criteria and a higher percentage of negative or inconclusive echocardiography results. Diagnostic delay might result in significant morbidity/mortality. Imaging modalities like 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT), prove to be an added diagnostic modality in such cases, thus assisting the accuracy of diagnosis by the modified-Duke-criteria. [^{18}F]FDG PET/CT can prove highly beneficial, provided proper preparation for adequate suppression of the physiological myocardial uptake is done prior to the scan, thus helping is semi-quantitative analysis of the infected focus. We herein, report a case of suspected infective endocarditis with known prior history of a prosthetic valve in situ where the diagnosis of infective endocarditis could not be established with conviction, despite the use of conventional modalities of imaging like 2D echocardiography. [^{18}F]FDG PET/CT proved its mettle by determining the primary site of infection, as well as metastatic extra-cardiac infective foci, and thus avoiding morbidity arising out of delayed diagnosis.

Key words: Extra-cardiac infection; Infective endocarditis; Treatment response; [^{18}F]FDG; PET/CT

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INTRODUCTION

Infective endocarditis (IE) is microbial infection of the endothelial surfaces of the heart or iatrogenic foreign bodies like prosthetic valves and other intra-cardiac devices. It results from metastatic infection, embolic phenomenon, or immune-mediated damage. An infected vegetation may form because of cascades of interactions between invading microorganisms and the host immune system. It has been established pathologically to be an infectious process since the 19th century. Sir William Osler was one of the first to suggest a unifying theory in 1885, Gulstonian lectures on malignant endocarditis, in which he mentioned that susceptible patients developed 'mycotic' growths on their valves followed by "transference to distant parts of microbes" [1, 2].

CASE PRESENTATION

49 years old woman, presented to the hospital, with history of intermittent fever of 2 months durations (Tmax-102°F), associated with chills, and mechanical low backache of 5 days durations. The patient also gave a history of loss of appetite, with significant weight loss, over last 2 months. The patient has been a known case of Rheumatic Heart disease (RHD) with mitral stenosis since 1990, who underwent open mitral valve repair in 1992, percutaneous transvenous mitral commissurotomy (PTMC) in 1995 and mitral valve replacement (MVR) in 2005. She had a history of undergoing dental surgery (root canal therapy), 7 days prior to onset of fever. There was no evidence of infective endocarditis or fresh rheumatic activity. Fundus examination was normal. Abdomen examination revealed a palpable spleen 1 cm below the left costal margin. CVS examination revealed an audible prosthetic valve click. Rest of the systemic examination was essentially normal.

Her preliminary investigations revealed Hemoglobin of 8.3gm/dl, TLC=13100 cu/mm, polymorphs 82%, ESR- 89mm fall at 1 hour, CRP=99mg/L, PT-INR:2.4 (on Acitrome 2 mg/day). Peripheral blood smear showed a normocytic normochromic anemia, with leucocytosis and left shift. Serum ferritin was 2782 ng/ml. Urine and blood cultures were sterile. Tuberculin skin test was negative. Trans-thoracic echocardiography (TTE) showed prosthetic valve in situ, trivial paravalvular leak, no mitral regurgitation (MR), no vegetations, no RWMA/LVEF 60%, which was subsequently confirmed on trans-esophageal echocardiography (TEE). USG abdomen showed mildly enlarged spleen (13.6 cm) with multiple hypo-echoic lesions. Repeat blood cultures were taken, out of which 2 sets grew Streptococcus angionosus, and 3 sets blood cultures grew Pediococcus pentosaceus. **[**18F]FDG PET/CT was done in view of high suspicion of IE. Protocol followed was diet restriction (low carbohydrate with high fat and proteins) for 48 hours prior to study to suppress the physiological myocardial uptake. It showed intense metabolic activity in periprosthetic region-posterior annulus (SUV max 10.8), anterior annulus (SUV max 12.15), enlarged spleen with hypodense lesions and **[**18F]FDG avidity, and **[**18F]FDG avidity in 5th lumbar vertebrae (LV-5) and paravertebral soft tissue [Figure 1]. The final diagnosis was prosthetic valve endocarditis managed with intravenous antibiotics for 6 weeks.

A repeat **[**18F]FDG PET/CT post 6 weeks of treatment showed entire myocardium revealing adequate suppression of physiological metabolic activity along with resolution of **[**18F]FDG avidity in spleen and existing vertebral sites [Figure 2].

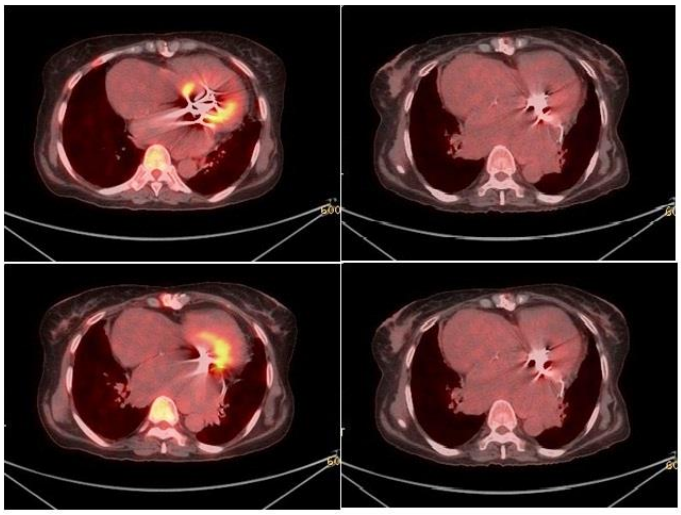
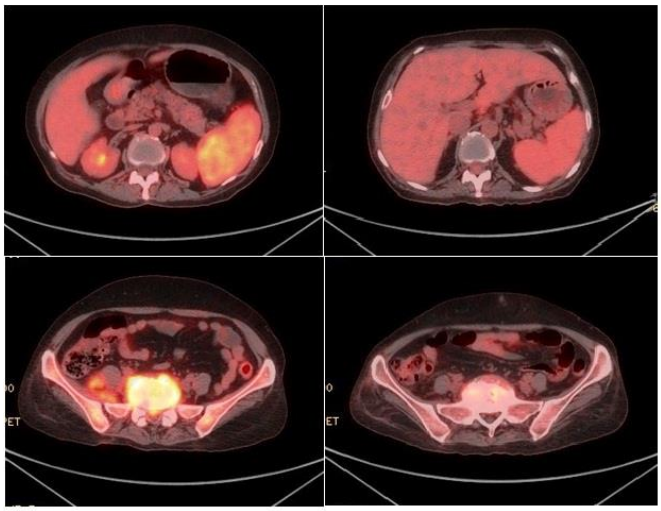


Fig 1. [18F]FDG PET/CT scan in axial section showing metabolic activity in the periprosthetic region that further shows resolution of metabolic activity post antibiotic therapy.



Fige 2. [18F]FDG PET/CT scan in axial section showing metabolic activity in hypodense lesion in spleen and in 5th Lumbar Vertebrae (LV-5) that further shows resolution post antibiotic therapy.

DISCUSSION

The incidence of IE is a little uncommon in the era of modern medicine, with a systematic review, observing a global burden of IE to be ranging from 1.5-11.6 cases per 100,000 person-years, however despite the best available therapy, mortality rates continue to be high. In a European heart survey, 26% of the patients were older than 70 years; however, in India it is commoner in the younger age groups. Some studies in Indian patients indicated that 76% of the patients with IE were younger than 40 years (median age 27.6 ± 12 years) [3, 4]. Streptococci and staphylococci have collectively accounted for approximately 80% of IE cases in the world. Healthcare-associated IE has been accompanied by an increase in the prevalence of Staphylococcus aureus and coagulase-negative staphylococci. Enterococci are the third leading cause of IE and are increasingly linked to health care contact. In India where RHD is more prevalent, Streptococci viridians is the most common causative organism, responsible for 30–65% of native valve endocarditis (NVE), while Staphylococcus aureus is the single most common cause of IE, in about 40% cases of health care associated endocarditis, with properties to invade an intact endothelium. Despite a large agricultural population, large livestock and zoonosis, IE with fastidious and atypical pathogens like Coxiella, Brucella and Salmonella typhimurium are rarely diagnosed in India. As these cannot be cultivated in conventional culture media, bacterial culture negative endocarditis (BCNE) is an emerging problem [5]. Streptococcus angionosus in one of our case belongs to subgroup of viridans streptococci (gram negative, catalase negative), present as normal flora in humans (oral cavity, stools) and is an uncommon cause of endocarditis in native wall but can cause endocarditis in prosthetic valve [6]. Pedioccoccus pentosaceus is gram-positive, non-motile, non-spore forming bacterium, and is categorized as a “lactic acid bacteria”, usually non-pathogenic, Pedioccoccus pentosaceus is commonly found in fermented plants such as pickled vegetables and silages few case reports of bacteremia and endocarditis have been reported. Opportunistic Pedioccoccus pentosaceus infections have been rarely reported [7].

The clinical diagnosis of IE has been based on the modified DUKE criteria, based on clinical symptoms, blood microbiologic cultures and echocardiography with a reported sensitivity value of 80%. The diagnosis relies heavily on the diagnostic accuracy most common imaging technique is TTE and TEE, and both should be performed in all patients with suspicion of IE. ECG gated cardiac CT angiography (CTA) provide high resolution images for visualization of complications of infective endocarditis such as pseudo-aneurysms, fistulas, valve perforation, abscess, valvular dehiscence, and vegetation. Presently, TEE and CTA are the first line imaging choices. However, almost 30% of cases of PVE show normal or inconclusive echocardiography. The ESC guidelines state that [18F]FDG PET/CT may diagnose infective endocarditis classified in the ‘‘possible’’ category of the modified Duke criteria and appreciate the peripheral emboli and metastatic infective foci. However, AHA guidelines observe that more studies would be required to determine the roles of [18F]FDG PET/CT [8, 9]. The most used radiopharmaceutical for infection imaging is [18F]FDG, which is actively incorporated by activated leukocytes, that accumulates at the site of infection. It comments on the metabolic as well as structural abnormalities and differentiates them from surrounding healthy tissues. Its uptake depends on the metabolic activity and is proportional to the quantity of glucose consumed [10].

Several studies report that [18F]FDG PET/CT has higher rates of detection than echocardiography for PVE; with sensitivity values of 73-85%, specificity approaching 80% and a positive predictive value of 85%. Most of the existing literature has proposed considering the combination of modified Duke Criteria and [18F]FDG PET/CT that would achieve a sensitivity of 97% for early diagnosis of PVE with little loss of specificity. In addition, the utility of [18F]FDG PET/CT in monitoring the response to antimicrobial treatment in patients not selected for cardiac surgery has been reported showing an early reduction within the quantified metabolic activity in cases of appropriate antibiotic coverage. Another advantage of this imaging system is that it can detect peripheral septic emboli secondary to IE (intestinal, spleen, etc.), although there are certain limitations within the detection of stroke emboli, because the physiological uptake of glucose by the brain is considerable and emboli during this location are usually smaller than 5 mm, which is at the spatial resolution threshold of the present PET/CT scanners [11].

In our case, we observed peripheral infected septic involvement of spleen and vertebrae. In a study by Vos et al. embolic/metastatic events had incidence of 51% during infective endocarditis, however not associated with significant mortality. The embolic/metastatic sites involved the central nervous system, spleen, kidney, lung, liver, bone and joint, iliac or mesenteric arteries [12].

Certainly, this imaging technique has other limitations due to physiological distribution, so proper preparation must be ensured. False positives results can be in situations like postoperative inflammation in patients who have undergone cardiac surgery recently or certain disorders like tumors, active thrombi, soft atherosclerotic plaques, or vasculitis. Various protocols are available and mentioned in literature that mentions preparation and procedures to suppress physiological uptake of [18F]FDG by myocardial tissue. Therefore, preparation to promote free fatty acid metabolism and suppress physiologic glucose metabolism is necessary for successful imaging to appreciate the pathological metabolic activity. Dietary carbohydrate intake stimulates endogenous insulin secretion, which activates the predominantly expressed glucose transporter GLUT4 in normal myocardium and allows glucose to be the preferential substrate for consumption. However, in the absence/low levels of carbohydrates and insulin, the myocardium uses free fatty acids for energy. The inflammatory cells express GLUT1 and GLUT3, with increased glucose consumption. After entering a cell via a glucose transporter, [18F]FDG is trapped by phosphorylation, which is the basis of metabolic imaging. Metabolically active inflammation or granulomatous disease may be identified after adequate suppresses physiological myocardial uptake. The suppression of myocardial uptake is classified in three different sub-groups:- less or equal to liver (complete.), focally above the liver (partial), diffusely superior to liver uptake (absent) [13].

In a study by Jiménez-Ballvé et al., the criteria applied for classifying the findings as positive/negative for IE were based on (a) visual analysis of only PET images with attenuation-correction (AC PET images); (b) visual analysis of both AC PET images and PET images without AC (NAC PET images); (c) qualitative analysis of NAC PET images; and (d) semi-quantitative analysis of AC PET images. [18F]FDG PET/CT was considered positive for IE independently of the intensity and distribution of [18F]FDG uptake. The gold standard was the Duke pathological criteria (if tissue was available) or the decision of an endocarditis expert team after a minimum 4-month follow-up [14].

The 2015 European Society of Cardiology guidelines, mentions that abnormal uptake of [18F]FDG detected by PET/CT around prostheses implanted for more than three months was considered as a replacement major criterion in patients with suspected PVE, and an algorithm including echocardiography and [18F]FDG PET/CT was proposed. Considering these studies, we considered our patients an appropriate candidate for [18F]FDG PET/CT, as echocardiography could not pick up the reason for infection in these two cases and the correct diagnosis was vital for the best treatment. [18F]FDG PET/CT have implications in refining indications for surgery related to the prevention of embolic events and to persistent infection during the acute phase of IE [15].

The limitation in our study can be either overestimation or underestimation of SUV max values. Metallic implants can cause streak and band artifacts in PET/CT, which may reduce diagnostic quality of the CT image and also radiotracer uptake quantification is altered by feigning regions of high density, bright band artifacts can lead to overestimation of tracer uptake, while dark band artifacts in regions of low tissue density, leads to underestimation of tracer uptake [16].

CONCLUSION

This case report serves as an example to demonstrate the utility of [18F]FDG PET/CT in cases of high suspicion of PVE with negative echocardiogram. Semi-quantitative analysis and visual analysis including NAC images should be done simultaneously for differentiating between normal and pathological findings to comment on infective foci. The whole-body scans prove beneficial because we have seen metastatic infective sites in spleen and bone. [18F]FDG PET/CT scan improves the sensitivity of modified Dukes criteria in case of infective endocarditis

especially when transthoracic/transesophageal echocardiography is inconclusive. A repeat scan can be performed post completion of antibiotic therapy to comment on the metabolic activity of disease and treatment response. However, more studies and data need to be generated on this for generalized implementation.

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