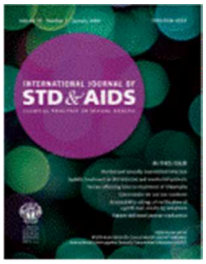

18F-Fluorodeoxyglucose positron emission tomography-computed tomography imaging in HIV-infected patients with lymphadenopathy, with or without fever and/or splenomegaly

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Short title: ^{18}FDG PET-CT imaging in HIV-infected patients

Key words: fever, lymphoma, infection, lymph node biopsy, HIV infection, PUO, Kaposi sarcoma, Castleman disease, ^{18}F-FDG PET-CT imaging

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Abstract

We audited whether ^{18}F-Fuorodeoxyglucose positron emission tomography-computed tomography (^{18}FDG PET-CT) imaging could discriminate between different diagnoses in HIV-infected patients presenting with lymphadenopathy, with or without fever and/or splenomegaly. Maximum standardised uptake (SUV_{max}) values were similar in lymphoma and mycobacterial and fungal infections, and were lower but similar in those with HHV 8-associated disease and HIV-associated reactive lymphadenopathy. Nodal ^{18}FDG avidity, with SUV_{max} ≥10, excluded diagnoses of HHV 8-associated disease and miscellaneous conditions, and HIV-associated reactive lymphadenopathy was additionally excluded in those who had undetectable plasma viral loads. This audit suggests ^{18}FDG PET-CT imaging did not permit discrimination between specific diagnoses, but has utility in identifying lymph nodes with increased avidity that could be targeted for biopsy and in ruling out significant pathology.

Introduction

The immunosuppressed HIV-infected patient can present with lymphadenopathy, with or without a fever and/or splenomegaly [1]. The differential diagnosis for this presentation is wide, and includes Hodgkin and non-Hodgkin lymphoma, human herpesvirus 8 (HHV 8)-associated disease, including Kaposi sarcoma (KS) and multicentric Castleman disease (MCD), *Mycobacterium tuberculosis*, disseminated *Mycobacterium avium* complex, leishmaniasis and histoplasmosis [1–3], as well as other conditions such as metastatic carcinoma and HIV-associated "reactive" lymphadenopathy. Definitive diagnosis often requires tissue sampling with histology and/or microbiological culture in addition to traditional investigations. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}FDG PET-CT) hybrid imaging, already widely used in the diagnosis, staging and monitoring of malignancies, particularly lymphoma, is increasingly used to image infectious and inflammatory disorders in both immune-competent and immune-suppressed individuals [1, 4–11]. We audited whether ^{18}FDG PET-CT could aid in discriminating between diagnoses in HIV-infected patients presenting with lymphadenopathy, with or without fever and/or splenomegaly.

Methods

Consecutive patients who presented with lymphadenopathy, with or without fever and/or splenomegaly, at the HIV service at Mortimer Market Centre (MMC) and University College Hospitals (UCLH) London between January 2008 and December 2016 and who underwent ^{18}FDG PET-CT scanning as part of routine clinical investigation were identified from the UCLH Clinical Data Repository (CDR) system. Information collected from the CDR and the patient's clinical case notes included their presenting symptoms and signs, the maximum standardised uptake value (SUV_{max}) in node(s) or other tissue on ^{18}FDG PET-CT imaging, CD4 count, plasma HIV load, and whether the patient was receiving antiretroviral therapy (ART) at the time of diagnosis. The diagnosis of lymphoma, HHV 8-associated disease and HIV-associated reactive lymphadenopathy was made histologically, while that of mycobacterial and fungal infections was made by microbiological culture, as previously described [12]. In each patient ^{18}FDG PET-CT scanning was done prior to tissue sampling, and before results of microbiological culture were available. Patients in whom a tissue diagnosis of malignancy had been made and who subsequently underwent ^{18}FDG PET-CT scanning for staging were

excluded, as were those with undifferentiated fever, or pyrexia of undetermined origin (PUO). Results were analysed using Mann-Whitney and Kruskal-Wallis tests to compare SUV_{max} values among different patient groups. GraphPad Prism Version 6.0h (GraphPad software, Inc, La Jolla, CA, USA) was used for statistical analysis; $p<0.05$ was regarded as statistically significant.

Results

One hundred and twenty patients (88 men) presented with lymphadenopathy, with or without fever and/or splenomegaly, and underwent ^{18}FDG PET-CT. Figure 1 shows the clinical features at presentation. Patients were aged 42 years (33–48) [median (interquartile range: IQR)]. Forty-five patients were receiving ART and had an undetectable plasma HIV load (<50 copies/ml) [median (IQR) CD4 =400 (200–520) cells/µl], while 17 others were receiving ART but had detectable viral loads [median (IQR) =1700 (110–2850) copies/ml, CD4 =200 (155–340) cells/µl]. Fifty-eight patients were not receiving ART and had detectable viral loads [median (IQR) HIV plasma load =155,000 (15,250–550,000) copies/ml, and median (IQR) CD4 =185 (80–360) cells/µl].

The final diagnosis was HIV-related reactive lymphadenopathy in 43 patients, lymphoma in 27 (Hodgkin lymphoma in 13, diffuse large B-cell in 7, Burkitt in 3, plasmablastic in 3 and T-cell in 1), HHV 8-associated disease in 19 (KS in 5, MCD in 7 and KS with MCD in 7), mycobacterial infection in 14 (*M. tuberculosis* in 8, *M. avium* complex in 6), and fungal infections in 4 (*Cryptococcus neoformans* in 3, histoplasmosis in 1). Thirteen patients had a wide range of miscellaneous conditions: these were adult-onset Still's disease, sclerosing peritonitis, intra-abdominal sepsis, metastatic adenocarcinoma, reflux oesophagitis/benign colonic polyp, lobar pneumonia, visceral leishmaniasis, necrotizing granulomatosis, nodular hepatic fibrosis secondary to schistosomiasis, toxoplasmosis, and nodular hepatic fibrosis/portal hypertension with thyrotoxicosis/thyroiditis, each in one patient, and self-limiting febrile episodes with lymphadenopathy in two patients.

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SUV_{max} values were similar in lymphoma and mycobacterial and fungal infections and were lower but similar in those with HHV 8-associated disease and HIV-associated reactive lymphadenopathy. Individuals with miscellaneous (largely non-infectious and non-malignant

conditions) had low SUV_{max} values (Table 1). Across all diagnoses, there were statistically significant differences in median SUV_{max} when lymphoma was compared with HIV reactive lymphadenopathy (p=0.0007) and with HHV 8-associated diseases (p=0.0008), and when mycobacterial infection was compared with HIV reactive and HHV 8-associated diseases (p=0.004 and p<0.0001, respectively). No statistically significant differences were found between the other groups of diagnoses. Within each diagnostic group, median SUV_{max} showed no significant differences in those with detectable and those with undetectable viral loads (Table 1). Among all patients, nodal FDG avidity, with SUV_{max} ≥10, excluded diagnoses of HHV 8-associated disease and miscellaneous conditions, and HIV-associated reactive lymphadenopathy was additionally excluded in those in receipt of ART who had undetectable plasma viral loads. Reversal of the liver:spleen ^{18}FDG avidity ratio was observed more commonly among those with detectable viral loads but did not aid discrimination between diagnoses.

Discussion

This audit shows similar avidity of ^{18}FDG uptake, measured by SUV_{max}, in patients with lymphoma, mycobacterial infection and fungal infection; accordingly, ^{18}FDG-PET-CT imaging did not provide diagnostic information enabling discrimination between these diagnoses. A SUV_{max} ≥10 enabled HHV 8-associated disease and miscellaneous conditions to be excluded in all patients, and additionally, in those in receipt of ART who had undetectable plasma viral loads HIV-associated reactive lymphadenopathy could be excluded. This observation requires validation in prospective studies before it is used in diagnostic algorithms. In HIV infected patients different pathology may occur concurrently. This audit did not identify any features on 18FDG PET-CT imaging that suggested coexistence of dual or multiple pathology. The utility of ^{18}FDG PET-CT imaging was in identifying lymph nodes with increased avidity that could be targeted for biopsy and in excluding significant pathology. The limitations of this audit are first, it is from a single centre, and second, the sample size is small. Additionally, patients with undifferentiated PUO, and those with an established tissue diagnosis of malignancy prior to 18FDG PET-CT scanning were excluded.

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Table 1. Median SUV_{max} and diagnosis in 120 patients who underwent ^{18}FDG PET-CT imaging

Diagnosis (n)	SUV_{max} median (IQR)
HIV-related reactive lymphadenopathy (43)	5.6 (3.3–9.4)
Undetectable viral load (9)	3.7 (3.0–6.3)
Detectable viral load (34)	6.0 (3.3–9.7)
Lymphoma (27)	12.0 (6.5–14.0)
Undetectable viral load (17)	12.5 (6.8–18.1)
Detectable viral load (10)	12.0 (5.5–13.3)
HHV 8-associated disease (KS/MCD) (19)	5.7 (4.5–7.5)
Undetectable viral load (5)	5.7 (3.5–7.1)
Detectable viral load (14)	5.9 (4.3–8.9)
Mycobacterial infection (14)	10.9 (9.1–13.9)
Undetectable viral load (2)	8.7
Detectable viral load (12)	12.3 (9.2–14.6)
Fungal infection (4)	13.3 (6.4–20.6)
Undetectable viral load (3)	13.5 (4.2–23.0)
Detectable viral load (1)	13.2
Miscellaneous conditions* (13)	2.0 (2.0–6.1)
Undetectable viral load (9)	2.0 (2.0–7.1)
Detectable viral load (4)	2.0 (2.0–2.5)

Figure 1. Clinical features at presentation among 120 HIV-infected patients who underwent (^{8}FDG PET-CT imaging