PET/CT scanning with a high HIV/AIDS prevalence

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ABSTRACT

Positron emission tomography (PET) with [F-18]-fluoro-deoxy-glucose (FDG) has a well established and growing role in the management of most lymphomas. The interpretation of FDG PET scans in HIV positive patients is however challenging. This is largely due to scan changes giving a higher likelihood of false positive studies from both the direct effects of HIV and its treatment, and related to secondary HIV-related pathology. There is currently a need for further clinical research to evaluate to contribution of FDG PET in the management of HIV positive patients with lymphoma. In this paper existing studies related to FDG PET scanning in HIV positive patients will be reviewed, and potential pitfalls will be identified. These pitfalls can be avoided to some extent by the interpreter having a good clinical knowledge of the individual patients' condition, and an awareness of known scintigraphic patterns that can occur in these patients. PET remains a sensitive tool for the localisation of pathology, however when the exact nature of lesions has a direct bearing on patient management lesions need to be biopsied where possible. FDG PET can be particularly useful for the characterisation of brain lesions suspected to be related to primary central nervous system lymphoma.

1. Introduction

Positron emission tomography (PET) with [F-18]-fluoro-deoxy-glucose (FDG) currently has a well established and growing role in the management of a number of malignancies, including most lymphomas. This has been established from clinical research going back 20 years. Almost all of this literature arose from work performed in centres in the developed world. While the HIV pandemic is worldwide, the distribution of cases is skewed towards certain parts of the developed world. Currently 68% of adult cases are found in Sub-Saharan Africa [1], with 18% of cases in South Africa alone, a country with only 0.7% of the World's population [2]. This translates into a prevalence of 12% of the South African population. Given the non-specificity of FDG PET scanning to distinguish between FDG-avid tumour and inflammation/infection related to HIV, results obtained with FDG PET in countries with a relatively low HIV/AIDS prevalence may not necessarily be applicable in this context. In this paper we will attempt to better understand this potential challenge to the use of PET imaging in South Africa, by reviewing existing knowledge and suggesting future research directions.

2. Positron emission tomography

Clinical applications of PET are primarily in the fields of oncology, neurology and cardiology. In the developed world and more recently the developing world a rapid expansion in PET facilities has taken place, due to a dramatic increase in oncological indications since the 1990s. Positron emission tomography is an imaging technique that utilises positron emitting isotopes. The release of a positron, the anti-matter equivalent of an electron, and a neutrino in vivo results in the positron moving a short distance in tissue before undergoing mutual annihilation with a nearby electron. Based on the energy-mass formula $E = mc^2$, the energy of the two particles is converted into

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two 511 keV gamma rays that are released in opposite directions.

PET-CT cameras are a hybrid devices consisting of a PET camera with a number of rings of detectors which are able to detect the two gamma rays simultaneously thus positioning the source of the radio-isotope along a line between the two points of detection. The detection of millions of these events enables the generation of a three dimensional image of the distribution of the radio-isotope in the body. The CT component consists of a CT scanner immediately adjacent to the PET scanner. The complementary nature of the functional PET and anatomical CT images enhances the sensitivity and particularly the specificity of the technique, with improved anatomical characterisation and localisation of PET lesions. For example this can be essential to distinguish between normal physiological uptake in certain structures (such as brown fat) and abnormal pathological uptake in others (such as lymph nodes).

This paper will be limited to the discussion of PET-CT scanning using [F-18]-FDG which is currently the most important radiopharmaceutical used in PET scanning in general, and in the management of lymphomas in particular. The increased concentration of glucose transporter proteins and hexokinase enzymes results in a relatively increased accumulation of FDG in a large number of tumours [3]. FDG differs chemically from glucose in the absence of an oxygen atom and the addition of a fluorine-18 atom in position 2. This not only makes it possible to detect the molecule with a PET camera, but also alters its biochemical handling in vivo. Similar to glucose, FDG is taken up into cells and under the influence of hexokinase can be phosphorylated to FDG-6-P. Glucose-6-phosphate can be metabolized further whereas FDG-6-phospate cannot, nor can it be converted back to FDG and released from the cell. The chemistry of FDG therefore results in its accumulation and concentration, particularly in cells rich in glucose transporters and hexokinase.

Uptake of FDG is therefore a marker of increased glucose metabolism which in itself is relatively non-specific, typically being present in both neoplasia and areas of inflammation. As will be discussed later this presents both a strength and a weakness in the management of patients with HIV and lymphoma. Normal bio-distribution of FDG results in uptake in the brain, heart, liver, gastro-intestinal tract, urinary system, and in muscles (Fig. 1). Scans are normally performed on an outpatient basis, and patients are able to leave immediately once the imaging has been completed.

3. PET-CT in lymphoma

Literature examining the value of PET and PET-CT scanning is subjects with HIV covers a number of conditions, including a specific literature on AIDS Dementia Complex (ADC) as well as work with a variety of PET tracers measuring a number of aspects of in vivo function. This paper is however limited to the main role of PET-CT in clinical haematological practise, namely FDG PET-CT scanning of patients with lymphomas. FDG PET has a well established role in the management of most lymphomas during initial staging, restaging after completion of therapy, and for the

Fig. 1. Maximal intensity projection of a FDG PET scan showing normal FDG biodistribution.

detection of suspected disease recurrence. Currently there is also active and exciting research into its potential role in individualising therapy.

When used to stage Hodgkin's disease (HD) and aggressive non-Hodgkin's lymphoma (NHL) after initial diagnosis, PET has been shown to have an excellent sensitivity and specificity [4,5]. Furthermore in the general patient population a false positive rate of only 1–13% was found. A meta-analysis of a number of studies found that compared to conventional imaging disease was upstaged in 8–17% of patients, and downstaged in 2–23% of patients. This results in alterations of patient management in 10–20% of patients. Importantly the availability of a pre-treatment baseline scan is also key to the correct interpretation of subsequent post-treatment scans.

Following completion of therapy PET also has been shown to play a key role in assessing the response to therapy. In this scenario for the detection of residual disease PET has been shown to have a sensitivity of 72% (61–82%), and a specificity of 100% (97–100%) for NHL, while the sensitivity is 84% (71–92%) and specificity is 90% (84–94%) for HD [6]. Consequently routine use of PET is recommended in aggressive NHL (especially diffuse large B-cell lymphoma) and HD, where available, with interpretation based on the new Cheson Guidelines for end of treatment evaluation [7]. Post therapy PET is also a powerful indicator of individual patient's future prognosis [8,9]. Results may be less impressive following biological therapy however, where ongoing positive studies may present challenges to their interpretation.

PET can play a valuable role in confirming and localising lymphoma in patients with suspected disease recurrence based on clinical, biochemical or radiological findings [10]. However routine surveillance of patients in remission is controversial. Currently only limited data is available [11], and routine surveillance of patients in remission is generally not recommended given the resultant increased cost, increased radiation dosimetry, and the high proportion of false positive studies. Currently exciting work within trials is examining the potential value of FDG PET scanning during therapy. This has the potential to allow clinicians to individually tailor therapy based on early interim PET results, with a view to reducing overtreatment and side effects in patients for whom chemotherapy is ineffective, or when additional chemotherapy is unnecessary. It may also be useful to identify those patients for whom more aggressive therapy is indicated.

However the body of literature discussed above is based on studies performed with patients who were almost exclusively HIV negative. The question immediately arises to what extent are these conclusions are valid in a patient population in which a significant proportion of patients are HIV positive? Currently little data is available to provide a definitive answer this question, but in order to begin to address it we need to review existing knowledge on PET scanning in HIV positive subjects. Challenges affecting the interpretation of PET studies in HIV positive patients can be broadly divided into two groups: (1) changes to the scan related directly to HIV infection and its treatment, and (2) changes to the scan related to secondary HIV-related pathology.

4. Scan changes related directly to HIV infection and its treatment

Direct effects of HIV and its treatment can result in changes on PET studies which can confound their interpretation. These changes can result in false positive studies due to areas of inflammation, or scan patterns related to HAART. These are set out in a recent review [12].

4.1. Benign lymph node uptake

Following HIV infection, binding of HIV to CD4 T-lymphocytes leads to homing of lymphocytes to lymph nodes and subsequent apoptosis [13]. This results in lymphadenopathy clinically and eventually in loss of lymph nodes [14]. This involvement of lymphoid tissue following HIV infection follows a predictable anatomical sequence from the upper to the lower torso. Lymph node activation on PET scans has corresponding FDG uptake patterns which can be divided into 3 phases: (1) an acute phase involving the head and neck, (2) a mid phase with generalised involvement, and (3) a late phase with involvement of abdominal lymph nodes [15]. This can result in FDG PET studies which can be interpreted as false positive for lymphoma (Fig. 2).

For HIV positive patients at risk for developing lymphoma the distinction between benign and malignant lymph node involvement is crucial for their correct management. Currently only limited data is available examining the influence of this phenomenon in these patients.

Fig. 2. Coronal slice of FDG PET scan showing extensive FDG uptake in lymph nodes in a patient with HIV related generalised lymphadenopathy. (Image courtesy of Sathekge et al. [21]).

One study examined 6 patients with lymphoma. Four out of 16 scans (25%) showed FDG uptake in lymph nodes shown on subsequent biopsy to be benign [16]. Another study examined 13 pts with Burkitt lymphoma. Here 7/13 (54%) patients had FDG uptake believed to be related to HIV lymphadenopathy, given the rarity of lymph node involvement in this disease [17].

There is a high-overlap in mean specific uptake value (SUV) values between in malignant lymph nodes, and patients with HIV-related lymphadenopathy thus limiting the clinical value of SUV values at the individual patient level. In the same study, CT also did not prove useful for this purpose [18]. The degree of FDG uptake in lymph nodes is however related to the viral load [19,20], and inversely related to the CD4 count [21]. Therefore the availability of this information may assist with the interpretation of PET studies, and in order to minimise false positive studies the viral load should ideally be zero. Where doubt exists, the biopsy of affected lymph nodes is required when the outcome will affect patient management.

4.2. Lipodystrophy

Highly active antiretroviral therapy (HAART) may result in lipodystrophy, a chronic and progressive syndrome of peripheral fat loss and/or abdominal obesity, and hyperlip-

idaemia [22,23]. It is also associated with hyperinsulinaemia, increased C-peptide, insulin resistance, impaired glucose tolerance. Lipodystrophy is reported in up to 60–80% of patients on HAART, and is especially associated with stavudine, and on PET demonstrates increased FDG uptake in subcutaneous adipose tissue (Fig. 3) [24]. Without knowledge of this phenomenon, this uptake pattern may be misinterpreted as diffuse soft tissue inflammation, or even as a technical fault with attenuation correction. The potential role of FDG PET in monitoring response to various treatment options aimed at reducing insulin-resistance in lipodystrophic HIV-patients under HAART warrants further investigation [25].

4.3. Thymic uptake

HAART may also induce what appears to be a thymic reactivation in adults [26]. This must also be interpreted in the light of evidence that thymic uptake is often also seen well into adulthood on PET in HIV negative patients [27]. Without this knowledge these studies may be falsely reported as being positive for disease in the anterior mediastinum.

5. Scan changes related to secondary pathology

Impaired immunity related to HIV infection leads to increased susceptibility to infection by pathogens such as cytomegalovirus, cryptococcus neoformans, and tuberculosis [28]. In addition there is increased vulnerability to developing malignancies such as lymphoma, Kaposi's sarcoma, and anogenital cancers [29], related to impaired host immune surveillance, increased infection with oncogenic viruses, and facilitation of tumour angiogenesis and KSHV transmission by HIV-1 encoded proteins [30].

5.1. Infection

The patient's condition affects the diseases that they are most susceptible to, and depending on CD4 levels, the composition of a FDG PET differential diagnosis changes. Thus different pathogens typically affect HIV positive patients at different stages of the disease. For example tuberculosis, salmonella, shigella, and corynebacterium infection typically occur with a CD4 count of 200–500 [31], while cryptosporidiosis and pneumocystis jiroveci normally occur when the CD4 count drops below 200, and cytomegalovirus and atypical mycobacterial infections when the CD4 count drops below 60 [32]. While tuberculosis infection commonly occurs with a CD4 count of 200–500, it can occur at any stage of the disease.

Immunocompromised patients with infections often present a challenge clinically, often presenting atypically. Similarly it is important to identify infection in these patients as this information is likely to affect their management with chemotherapy, HAART, and antimicrobials. In this context PET can be a powerful modality to identify and localise sites of infection. However since lymphoma presents on FDG PET in similar ways to tuberculosis, the most devastating opportunistic infection in HIV; lymphadenopathy can no longer be used as a distinguishing imaging feature. In one series there was a high-overlap in SUV-mean values between in FDG uptake by malignant lymph nodes and lymph node positive for tuberculosis [18].

However, tuberculosis can present with extrapulmonary disease, and PET has been shown to be accurate to detect this [33]. In addition PET/CT has demonstrated more extensive tuberculous lymphadenitis than conventional imaging, as well as directly suggesting sites for biopsy [34]. While a new strategy for the application of FDG
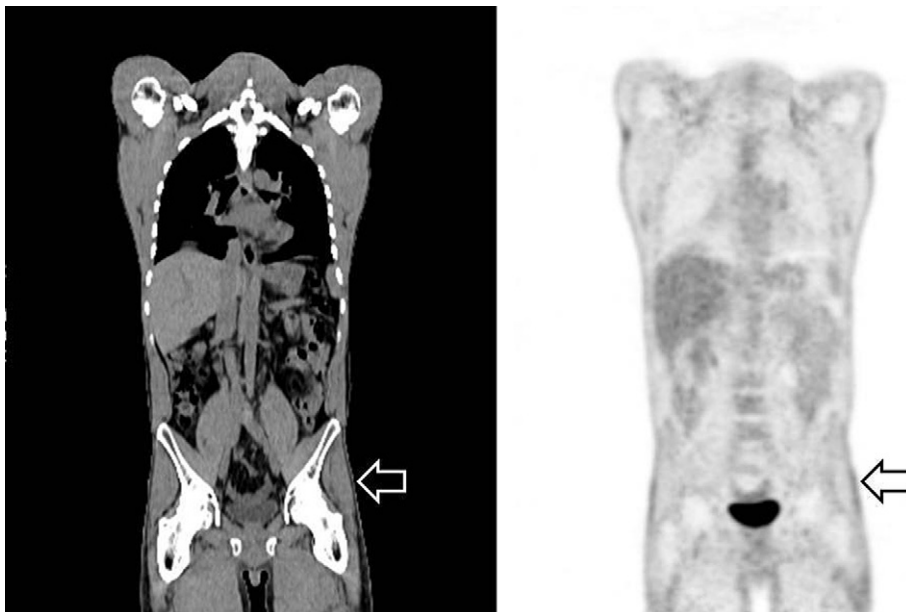

Fig. 3. Coronal slice of FDG PET scan showing uptake of FDG in subcutaneous fat (arrows) in a HIV positive patient with lipodystrophy due to HAART.

PET/CT examinations in AIDS is critical, interpretation is therefore severely compromised without detailed clinical information from the clinician, resulting in reports without any coherent conclusion and without being able to assist in managing the patient. Currently there is a paucity of knowledge and more research needed to examine the potential role of PET for the detection of occult infection, and the monitoring of therapy, at least in selected subgroups of these patients.

PET is therefore useful to detect and localise sites of occult infection or inflammation, but because this uptake is frequently impossible to distinguish from uptake in sites of lymphoma there is a decline in specificity for the diagnosis of lymphoma. This is true too for anatomical imaging with CT scans showing many false positive studies related to infection in HIV positive patients, with two thirds of abdominal lymph node masses being infective in one study [35]. When interpreting PET/CT scans some clues can assist in suggesting a distinction between lesions related to infection as opposed to those caused by lymphoma. Ways of increasing specificity include correlation of the PET with the CT study. In some situations anatomical imaging can provide lesion characteristics that are strongly suggestive of infection or tumour. Serial scanning can also be useful by demonstrating the disappearance of lesions following chemotherapy or antimicrobial drugs. This may also manifest with different lesions behaving differently in the same patient. For example lymphomatous lesions may improve or disappear following chemotherapy, while other lesions deteriorate or appear at new sites. These new or deteriorating lesions are likely to be behaving differently because they represent a different type of pathological process such as infection, or another more resistant cancer strain (Fig. 4). While this information can go some way to enhancing the specificity of the study, biopsy remains the only reliable way of distinguishing infection from tumour.

5.2. Primary central nervous system lymphoma

In HIV positive patients with central nervous system lesions it is critical to distinguish primary lymphoma from benign conditions such as toxoplasmosis and tuberculosis.

This cannot be reliably achieved using anatomically based techniques such as CT or MRI. Several studies using qualitative and quantitative evaluation of PET however have demonstrated the effective separation of lymphoma with high uptake, from other benign conditions where uptake is lower [36–38].

6. Conclusion

The interpretation of FDG PET scans in HIV positive patients is complicated by false positive studies from both
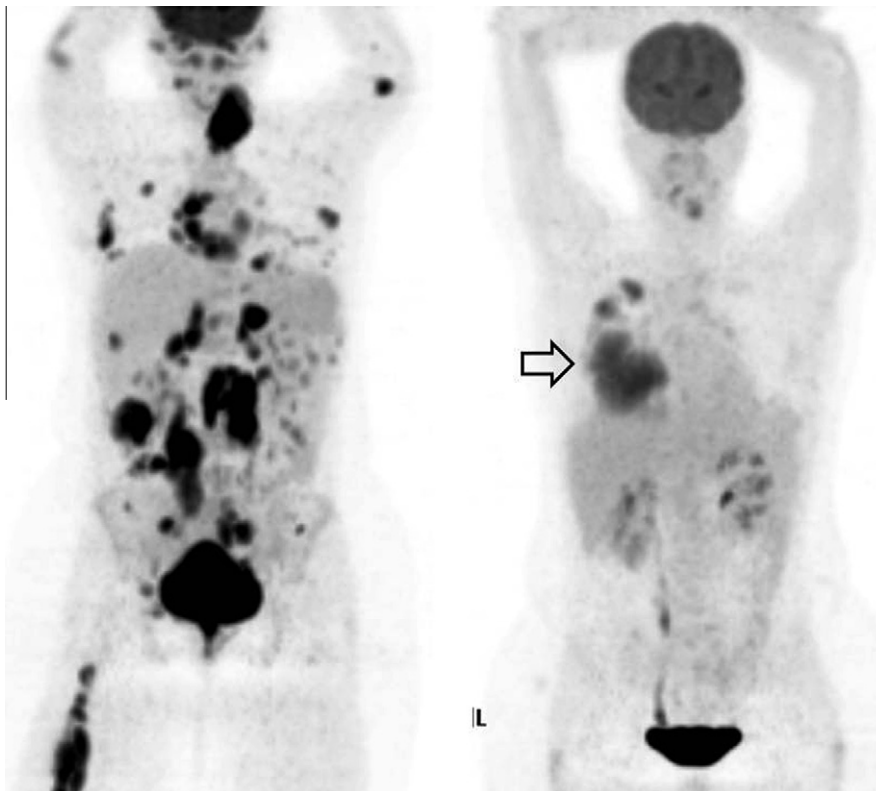

Fig. 4. Maximal intensity projection images of FDG PET scans of a HIV positive patient with lymphoma pre (left) and post (right) chemotherapy. On the post-therapy scan there is a dramatic response to chemotherapy, but a new area of FDG uptake is noted in the right side of the chest (arrow). This differing behaviour of the lesions suggests another pathology such tuberculosis.

the direct effects of HIV and its treatment, and due to secondary HIV-related pathology. These pitfalls can be avoided to some extent by the interpreter having a good clinical knowledge of the individual patients' condition, and an awareness of known scintigraphic patterns. PET remains a sensitive tool for the localisation of pathology, however when the exact nature of lesions has a direct bearing on patient management lesions need to be biopsied where possible. There is a need for further clinical research to evaluate to contribution of FDG PET in the management of HIV positive patients with lymphoma.

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