Differentiation of HIV-associated lymphoma from HIV-reactive adenopathy using quantitative FDG-PET and symmetry

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In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Mhlanga et al. [1] address the important challenge of differentiating between HIV-reactive lymphadenopathy and HIV-associated lymphoma using FDG PET/CT. What is more interesting about this study is the fact they rigorously assessed the quantitative PET metabolic metrics to distinguish these entities. The investigators evaluated nodal and extranodal visual qualitative metabolic scores, SUL-Max, SUL-Peak, CT nodal size, and PERCIST 1.0 threshold-based TLG and metabolic tumour volume (MTV), in 19 patients with biopsy-proven untreated lymphoma (16 with large B-cell lymphoma, 3 with Hodgkin lymphoma) and 22 patients with reactive adenopathy. The results of this study demonstrated that quantitative PET metrics performed significantly better than qualitative visual scores, although qualitative symmetry assessment was valuable. Both quantitative PET metrics and qualitative assessments of symmetry of uptake were also more robust than CT nodal size assessments. The investigators are therefore to be congratulated on achieving their aim and developing a potential practical approach, with the limitations also being interesting for future prospective studies.

Several reasons stated below make this topic remain the subject of hot debate even though a number of studies [2] have demonstrated the effectiveness of FDG PET in the evaluation of lymphoma and the escalating role of FDG PET/CT in the management of HIV-infected patients [3]. Lymphadenopathy is common in HIV-infected individuals as lymphoid tissue is a major target and reservoir of HIV [4]. The most common

conditions affecting the lymph nodes in HIV-positive patients are reactive changes, opportunistic infections (e.g. tuberculosis, TB), and malignant neoplasms (e.g. lymphoma). Lymphadenopathy may occur at any stage of HIV infection and can be complicated by mycobacterial infection which still remains one of the most common causes of lymphadenopathy in HIV-infected patients, especially in developing countries [3]. Yet persistent generalized lymphadenopathy often precedes the development of lymphoma and is indicative of an increased risk of lymphoma [4].

Current knowledge about HIV-associated lymphomas can be summarized as follows: (1) they are closely linked to oncogenic herpesviruses, namely Epstein-Barr virus and Kaposi sarcoma-associated herpesvirus; (2) they are predominantly aggressive B-cell malignancies (widely disseminated with frequent involvement of extranodal sites); (3) most are Burkitt lymphoma and diffuse large B-cell lymphoma; (4) Hodgkin lymphoma which is a non-AIDS-defining malignancy has been shown to be increased in incidence in the setting of HIV infection [1, 3].

Immune inflammatory reconstitution syndrome (IRIS) in HIV-infected patients after initiation of highly active antiretroviral therapy (HAART) has been increasingly recognized. IRIS is defined as a paradoxical worsening or unmasking of infections, autoimmune diseases or tumours after initiation of HAART, and is usually seen when the initial CD4 count is low. The diagnosis of IRIS is often challenging as the differential diagnosis is complex, including opportunistic infection, drug failure/toxicity or malignancy [5]. Relevant to this article, the most common symptoms seen in IRIS are fever, lymphadenopathy and pulmonary symptoms [6] which resemble symptoms seen in patients with HIV-associated lymphoma. The interpretation of FDG PET/CT scans in patients with HIV infection and a low CD4 count is particularly challenging as a variety of infections and malignancies may cause increased FDG uptake [5, 7]. Hence, differentiation

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between reactive/inflammatory lymph nodes and malignant lymphoma is very challenging without histopathological investigation involving an invasive procedure. However, obtaining tissue for histology either by core needle biopsy or entire lymph node excision carries associated risks. If a biopsy is considered, the largest and most abnormal node (not necessarily the most easily accessible node) should be excised. Of importance, inguinal and axillary nodes may not be suitable for biopsy as they often show reactive hyperplasia. Therefore optimized imaging is critical.

In an effort to improve patient care, several approaches have been suggested to increase FDG PET/CT specificity in lymphomas. Some of the important methods are; quantification with SUV-max, qualitative assessments of symmetry of uptake, dual-time-point and concurrent FDG avid nasopharyngeal lesion [7–10].

- Unfortunately, there is considerable overlap in SUVmax between lymphoma and benign lymphadenopathy, causing difficulty in achieving a correct diagnosis from FDG PET data, thus limiting the clinical value of SUV at the individual patient level [8]. The degree of FDG uptake in lymph nodes is, however, related to the viral load [11], and is inversely related to the CD4 count [3]. Therefore the availability of this information may assist with the interpretation of PET studies, and in order to minimize false-positive studies, the viral load should ideally be nondetectable.
- A dual time-point FDG PET/CT scan is useful for differential diagnosis between lymphoma and benign lymphadenopathy, regardless of histological subtype. Nakayama et al. [9] have shown that dual time-point FDG PET/CT imaging may help determine whether there is any need to proceed to more invasive tests, such as biopsy, in an individual patient.
- Previous studies have shown that faint symmetrical FDG uptake observed at nodal sites is properly reported as simple adenitis. However, interpretation of PET scans is improved when relevant studies and clinical data are considered [7]. Similar findings have been observed by these investigators.
- Liu found that a coexistent FDG avid nasopharyngeal lesion and generalized lymphadenopathy on PET/CT imaging is indicative of a malignant lymphoma rather than benign lymphoproliferative disease or nasopharyngeal carcinoma [10]. However, Mhlanga et al. [1] found no significant difference in the nasopharyngeal region mean SUL-Max scores between patients with HIV-associated lymphoma and those with HIV-reactive adenopathy.

Despite these attempts, the optimum method for differentiating between HIV-reactive lymphadenopathy and HIV-associated lymphoma with ^{18}F -FDG PET/CT is unresolved,

and limitations have been recognized, particularly with regard to HIV-viraemic subjects, location of nodes and coinfection with TB. And these studies did not look at SUL-Max, SUL-Peak, CT nodal size, and PERCIST 1.0 threshold-based TLG and MTV. Furthermore, in none of them was a multivariable logistic regression analysis performed to attempt to identify a subset of relevant PET parameters that could potentially be used in routine practice to distinguish patients with HIV-associated lymphoma from those with HIV-reactive adenopathy. In HIV-associated lymphoma, the locations of increased FDG uptake that most frequently leads to false-positive results are the axillary, mediastinal and inguinal nodes and the lungs. The reason is probably the higher incidence of inflammation and hence inconclusive findings at these locations [11]. These observations are consistent with those described in the literature noting an association between the clinical stage of HIV infection and the pattern of lymphoid tissue activation [12, 13].

Although the study by Mhlanga et al. [1] demonstrated that the quantitative PET metabolic metrics and qualitative assessment of symmetry of nodal uptake appear to be valuable tools for separating lymphoma from reactive adenopathy in HIV-infected patients, there is still poorer diagnostic specificity in subjects with an abnormal immune virological status. Perhaps future prospective investigation of combined quantitative PET metabolic metrics (SUL-Max, SUL-Peak, and PERCIST 1.0 threshold-based TLG and MTV) and dual time-point FDG PET/CT would certainly be of interest in HIV-viremic patients (excluding those with TB), as some potential synergy may improve the accuracy. Since this is the first reported study to use SUL-Max, SUL-Peak, CT nodal size and PERCIST 1.0 threshold-based TLG and MTV in patients with HIV lymphadenopathy, this may also lead to utilization of these parameters in infection imaging to provide incremental prognostic information beyond detection/staging, and could be considered for risk stratification in such patients.

Although beyond the scope the study by Mhlanga et al. [1], there remain unanswered questions regarding the specificity of FDG in HIV-positive patients with TB and lymphoma. Previous studies including dual time-point FDG PET/CT failed to distinguish HIV-associated malignancy and TB [3]. Although very unlikely, it is unclear if the proposed quantitative PET metabolic metrics could improve this poor record. Furthermore, as noted by the authors, the mean splenic metabolic uptake was increased in the patients with lymphoma compared to those with reactive adenopathy. This finding would most likely overlap between TB and lymphoma. As mentioned above with IRIS, the correlation among clinical status, immune function and imaging findings in patients with HIV infection is not always linear, and the interpretation of imaging findings can be complicated by the effects of therapy, such as HAART [5, 6], perhaps this scenario can be improved by rigorous implementation of the quantitative PET metabolic metrics.

Once again we highlight the importance of this study and congratulate the authors on their work which offers a potential practical approach using quantitative PET metrics to distinguishing patients with HIV-associated lymphoma from those with HIV-reactive adenopathy. It is also important to note that there is no need to combine the quantitative PET metrics as the multivariate analysis did not show a significant improvement when compared with each individual PET metric. Hence, in routine practice, each of the individual quantitative PET metrics can be used alone. The authors also confirmed that qualitative symmetry assessment is valuable and more accurate in differentiating aviraemic HIV-positive patients with lymphoma from those with reactive lymphadenopathy. Thus in viraemic patients, findings are sometimes non-specific, making close interaction between the nuclear physician and clinician in using clinical correlation to refine differential diagnosis all the more important.

In the future, as well as refining some of the inclusion criteria and methodological aspects of this interesting approach, further work may clarify some of the other unanswered questions concerning this approach such as its use in HIV-infected patients with HIV viraemia, TB and IRIS. There will undoubtedly be interest in combining quantitative PET metabolic metrics and qualitative assessment in monitoring and follow-up as this may help to guide treatment and minimize long-term toxicity.

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