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Evaluation of malignancies and F18-FDG PET/CT imaging of patients living with HIV/AIDS in a university hospital

Mehmet Cabalak[a,*], Hasan Ikbal Atilgan[b]

[a] *Mustafa Kemal University, Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology, Hatay, Türkiye*
[b] *Mustafa Kemal University, Faculty of Medicine, Department of Nuclear Medicine, Hatay, Türkiye*

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Abstract

Aim: Human immunodeficiency virus (HIV) can cause tumoral changes in immune cells and lead to the development of AIDS-defining malignancies. As malignancies in HIV-infected individuals tend to be quite aggressive with a worse prognosis, making a definitive and early decision about HIV-related malignancies is very important. Therefore, the aim of this study was to examine HIV-related malignancies in HIV-positive patients and evaluate F18-FDG PET/CT results.

Materials and Methods: This single-centre, retrospective study was conducted on adult patients with HIV infection at a university hospital between January 2018 and December 2022. The demographic data, medication use, viral loads, and F18-FDG PET/CT results of the patients were accessed retrospectively from the automated hospital records system and patient files. F18-FDG PET/CT images of patients were evaluated for those with suspicion of cancer and staging of cancer.

Results: The study included 254 patients with median age (IQR) 33 (20) years, male sex: 81.9%. Malignancy was diagnosed in 3.1% (8/254) of HIV-positive patients. Non-Hodgkin lymphoma and Kaposi's sarcoma were the most common cancers. F18-FDG PET/CT was performed in 3.5% (9/254) of patients, of which 2.76% (7/254) had findings suggestive of malignancy. As a result of the biopsy, malignancy was detected in five of these patients, and HIV-related lymphadenopathy was detected in two. In two patients, there were no F18-FDG PET/CT imaging findings suggestive of malignancy.

Conclusion: F18-FDG PET/CT can be used in the evaluation of HIV-infected patients with suspected malignancy.

Introduction

Human immunodeficiency virus (HIV) is a lentivirus that infects the CD4 cells primarily, thus greatly weakening the own defence of the body against disease [1,2]. In acquired immunodeficiency syndrome (AIDS), the number of CD4 T-lymphocytes of the host's immunity decreases. Consequently, the development of generalized lymphadenopathy (LAP) is the indicator of disease activity [3-5]. Long-term immune dysfunction malignant changes occur in immune cells, resulting in the development of AIDS-defining cancers. The term "HIV-related malignancy" is used to describe the group of malignancies (both non-AIDS-defining and AIDS-defining malignancies) that are increasing in frequency among patients with HIV infection. Aggressive B-cell lymphomas, Kaposi's sarcoma, and invasive cervical malignancy have been recognized as AIDS-defining malignancies when they develop in HIV infected patients. In patients with HIV, all cancers are considered as non–AIDS-defining cancers except aggressive B-cell lymphoma, Kaposi's sarcoma, and invasive cervical cancer [6,7].

These type of cancers occurred in 30% or more of patients in AIDS patients before the improvement of effective anti-HIV treatment [8]. Cancer is the main cause of death in HIV infected patients in developed countries [9]. Fluorine 18-fluorodeoxyglucose (F18-FDG) PET/CT is used for diagnosis, staging, assessment of response to treatment, and restaging of tumors due to increase in glucose metabolism in most types of malignancies. F18-FDG PET/CT can detect metastases with a single whole- body imaging [10]. F18-FDG PET/CT is most often used in oncology, but glucose metabolism also increases in infectious or inflammatory conditions. Activated granulocytes, lymphocytes and macrophages also have increased SUVmax that indicates increased cell glycolysis [11].

As malignancies in individuals with HIV infection tend

*Corresponding author:
Email address: mehcab@yahoo.com (Mehmet Cabalak)

to be highly aggressive with poorer prognosis, it is crucial to make a definitive and early decision regarding HIV-associated malignancies [12,13]. Therefore, the aim of this study was to evaluate HIV-related malignancies in HIV-positive patients and examine the F18-FDG PET/CT results. To the best of our knowledge, there has been very limited research in Türkiye on the evaluation of malignancy in HIV-infected individuals.

Materials and Methods

Study population

This retrospective analysis, conducted in the Infectious Diseases Clinic of Hatay Mustafa Kemal University, was approved by the Non-Interventional Ethics Committee of Hatay Mustafa Kemal University Faculty of Medicine (date: 07.06.2023, decisions number: 15). All procedures were applied in accordance with the Declaration of Helsinki as revised in 2013.

The study included all of the patients aged >18 years who were followed up with a diagnosis of HIV in the Infectious Diseases and Clinical Microbiology Clinic of a single centre between January 2018 and December 2022. Patients were excluded from the study if they were aged <18 years, were co-infected with hepatitis B or C virus, or had a history of cancer before the diagnosis of HIV.

Variables and data collection

HIV-infected patients with suspicion or diagnosis of malignancy were scanned with the F18-FDG PET/CT automated system. Of the 254 patients followed up for HIV in this study, PET/CT was only used on nine patients with suspected LAP or staging of cancer.

For viral load determination of PLHIV, the HIV-RNA levels were studied using real-time polymerase chain reaction (Bosphore HIV-1 Quantification Kit, Anatolia geneworks, Turkey). The $CD4^+$ T lymphocyte counts were examined with the flow cytometry method.

The primary outcome of the study was the frequency of cancer and the F18-FDG PET/CT findings of suspected LAP or a diagnosis of cancer in HIV-infected patients.

Statistical analysis

The descriptive statistics were presented as median, and interquartile range (IQR), frequency, and percentage. The Chi-squared test was employed to assess categorical variables. The normality of numeric data was assessed using the Shapiro-Wilk test. Whole parameters distributed non-normal. Mann-Whitney U test was employed for comparisons involving data that is not normally distributed. The statistical analyses were conducted using the SPSS (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) 21.0 software package. $p<0.05$ was accepted as statistical significant.

Results

Basic characteristics of the sample and prevalence of malignancy

The study included 254 patients [median age (IQR) 33 (20) years, male sex: 81.9%]. Malignancy was diagnosed in 8 (3.1%) HIV positive patients after biopsy and histopathological examination. Of the 254 patients followed up for HIV in this study, PET/CT was only used on 9 patients with suspected LAP or staging of cancer. The median (IQR) CD4 count of the cases at the time of initial admission was determined as 457 (415) cells/mm^3.The median (IQR) HIV RNA at the time of first admission was 42,350 (132,590) copies/ml. Of the eight cases with malignancy, 6 (75%) were male, and 2 (25%) were female. Comparison of age, gender, CD4 and HIV RNA of patients with malignancy (n=8) and non-malignancy (n=246) is summarized in Table 1.

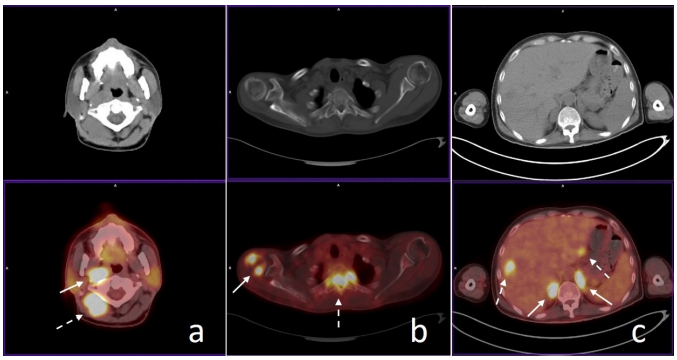

Figure 1. F18-FDG PET/CT was applied for the detection of the primary tumor after the observation of metastatic lesions in the liver and right adrenal gland on abdominal USG. PET/CT scan showing paravertebral (dashed arrow) and parapharyngeal hypermetabolic metastatic soft tissue masses (arrow) (a), right humerus (arrow) and T3 vertebrae lesions (dashed arrow) (b), liver (dashed arrow) and bilateral adrenal gland lesions (arrow) (c). The final diagnosis was Non-Hodgkin lymphoma after the biopsy of the cervical mass lesion.

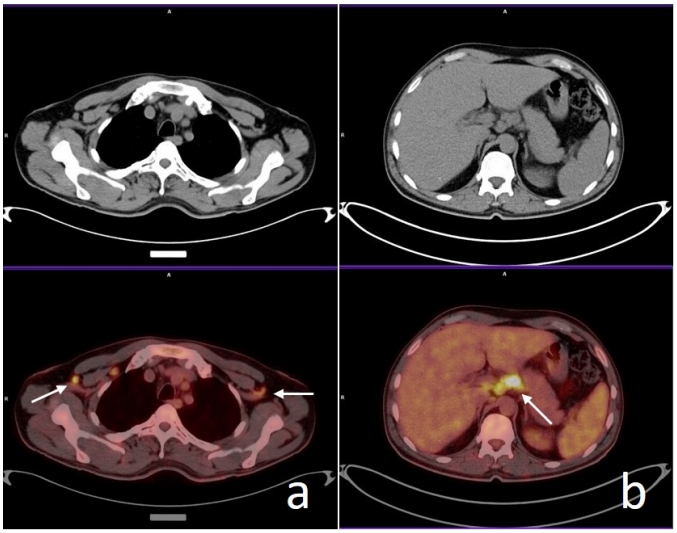

Figure 2. F18-FDG PET/CT was applied for the detection of the primary tumor after the observation of cervical and mediastinal lymphadenopathies on neck and thorax CT scans. PET/CT scans showing bilateral cervical (arrow) (a) and bilateral external iliac, obturator (dashed arrow) and inguinal lymphadenopathies (arrow) (b). The final diagnosis was Kaposi's sarcoma after the cervical lymph node biopsy.

Malignancy classification

AIDS-defining malignancy was detected in four cases, and non-AIDS-defining malignancy was detected in four cases. Non-Hodgkin lymphoma was diagnosed in two patients,

Table 1. Comparison of age, gender, CD4 and HIV RNA load of patients with malignancy and non-malignancy.

	Malignancy			
	No Median (IQR)	Yes Median (IQR)	Total Median (IQR)	p
Age	32.5 (20)	48 (22.5)	33 (20)	0.076[+]
Male/female	201(81.7%)/45(18.3%)	7(87.5%)/1(12.5%)	208(81.9%)/46(18.1%)	0.675[*]
CD4 count	462 (400)	200 (545)	457 (415)	0.058[+]
HIV RNA load	41360 (130928)	68300 (130470)	42350 (132590)	0.740[+]

[+]p was obtained from Mann Whitney U test, [*]p was obtained from Chi-Square test.

Table 2. Characteristics of patients with malignancy.

	Age	Gender	Type of malignancy	PET/CT Time of diagnosis	Time of diagnosis	Current status
1	29	M	NHL	+	Initial diagnosis	dead
2	52	F	Breast cancer	-	Follow-up	alive
3	31	M	Kaposi's sarcoma	+	Initial diagnosis	alive
4	54	M	Lung cancer	+	Follow-up	dead
5	28	M	Kaposi's sarcoma	+	Initial diagnosis	alive
6	54	F	NHL	-	Follow-up	alive
7	62	M	Colon cancer	+	Follow-up	alive
8	49	M	HL	+	Follow-up	alive

PET/CT: Positron Emission Tomography/Computed Tomography, NHL: Non-Hodgkin Lymphoma, HL: Hodgkin Lymphoma, M: Male, F: Female.

Table 3. Characteristics of patients who underwent PET/CT.

	Age	Gender	Sample Location	Pathology Result	PET/CT
1	29	M	Cervical LAP	NHL	Cervical mass, mediastinal, abdominal and pelvic LAP, liver and bone lesions (Figure 1).
2	24	M	-	-	Cervical, axillary and inguinal reactive lymph nodes.
3	28	F	-	-	Cervical, axillary and inguinal reactive lymph nodes.
4	31	M	Cervical LAP	Kaposi's sarcoma metastasis	Cervical, mediastinal, abdominalandpelvic LAP, pleural and subpleural metastatic lesions (Figure 2).
5	54	M	Lung biopsy	Lung cancer	Primary malignancy and wide spread metastases in the lung.
6	49	M	Periportal LAP	HL	LAP in the mediastinum and abdomen.
7	62	M	Colon biopsy	Colon cancer	Lymph node, liver and bone metastases.
8	57	M	Axillary LAP	HIV associated LAP	Cervical, mediastinal, axillary, abdominal, pelvic and inguinal LAP.
9	44	M	Right inguinal LAP	HIV associated LAP	Cervical, mediastinal, axillary, abdominal, pelvic and inguinal LAP (Figure 3).

LAP: Lymphadenopaty, M: Male, F: Female, PET/CT: Positron Emission Tomography/Computed Tomography, NHL: Non-Hodgkin Lymphoma, HL: Hodgkin Lymphoma.

Kaposi's sarcoma in two, and Hodgkin lymphoma, breast cancer, lung cancer and colon cancer each in one patient. The mean age of the patients with malignancy was 48 (28-62) years. The patients diagnosed with malignancy are summarized in Table 2.

PET/CT and antiretroviral therapy

PET/CT was performed in nine patients with suspicion of or a new diagnosis of malignancy (Five of eight patients with cancer). Three patients with cancer (One breast cancer, one Non-Hodgkin lymphoma and one Kaposi's sarcoma) did not undergo PET/CT. The demographic characteristics of the patients who underwent PET/CT are summarized in Table 3. Sample images of cases with PET/CT scans are shown in Figures 1-3. As the lymph nodes were thought to be reactive on PET/CT in two of nine patients due to the absence of pathological FDG accumulation in the lymph nodes, it was decided not to perform a biopsy but to follow these patients conservatively. Malignancy did not develop in either of these two patients during the follow up. Five of the remaining seven patients who underwent biopsy were diagnosed with malignancy, and HIV-associated LAP was detected in the remaining two. The diagnoses of these five patients were Hodgkin lymphoma, Non-Hodgkin lymphoma, Kaposi's sarcoma, lung cancer and colon cancer. The SUVmax of the LAP in the cases with Hodgkin and Non-Hodgkin were 8.56 and 27.71, respectively. The SUVmax value of the LAP in the patient with Kaposi's sarcoma was 8.25. The SUVmax of the LAP in the two patients with HIV associated LAP were 6.40 and

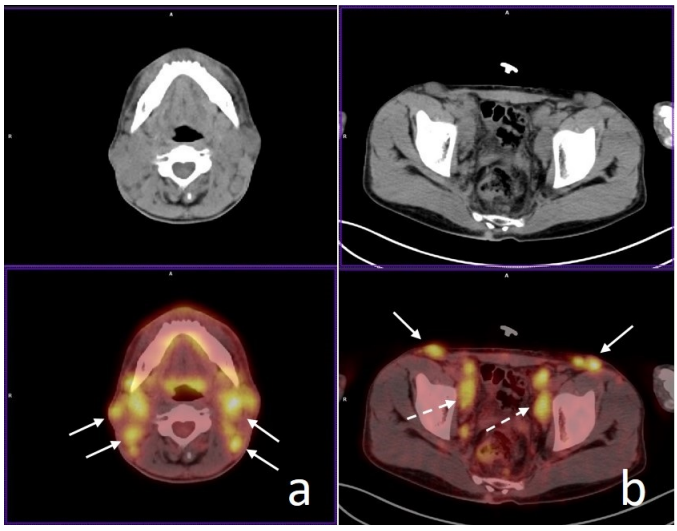

Figure 3. F18-FDG PET/CT was applied for the detection of the primary tumor after the observation of cervical and inguinal lymphadenopathies on USG. PET/CT scans showing bilateral axillary (arrow) (a) and paraaortic lymphadenopathies in the abdomen (arrow) (b). The biopsy from the inguinal lymph node was compatible with reactive lymph node.

5.05. The antiretroviral regimens (ART) used in the treatment of the cases diagnosed with malignancy were Tenofovir Alafanamide (TAF) + Emtricitabine (FTC) + Bictegravir sodium (BIC) in five patients, Tenofovir Disoproxil Fumarate (TDF) + Dolutegravir (DTG) + Emtricitabine (FTC) in two patients, Tenofovir Alafanamide (TAF) + Emtricitabine (FTC) + Elvitegravir /cobicistat (ELV/Co) in one patient.

Discussion

Although AIDS-defining malignancies have decreased with the use of antiretroviral therapies, one-third of the deaths in this population are due to malignancy [14,15]. A previous study found that the seroprevalence of malignancy in people living with HIV was 2.6% (48 patients) and 35 of these patients were diagnosed with AIDS-defining malignancy. While most AIDS-defining malignancies were diagnosed simultaneously with HIV, most non-AIDS-defining malignancies were diagnosed during patient follow-up [16]. In the current study, the seroprevalence of malignancy in people living with HIV was 3.1% (8 patients). Of these patients, four were diagnosed with AIDS-defining malignancy, three of which were diagnosed with malignancy concurrent with HIV. The high seroprevalence in this study may be due to the low number of patients.

LAP is frequent in HIV infection. Opportunistic infections, neoplasms, inflammatory conditions or reactive lymphoid hyperplasia may be the cause of LAP in HIV patients, whereas enlarged lymph nodes may be present at any stage of the disease [17,18]. Higher glucose metabolism is seen in the lymph nodes of HIV infected patients when compared with non-HIV infected individuals. High HIV RNA in the blood is associated with high viral replication in lymph nodes. LAPs have higher glucose utilization and dimension in lymphoma when compared with reactive LAP, but these conditions may overlap [19]. The etiology of LAP in HIV infected individuals should be defined. Fine needle aspiration biopsy of enlarged lymph nodes helps in the classification of the underlying disease such as neoplastic lesions, non-neoplastic lesions and opportunistic infections. Lymphoma is mainly seen in the fourth decade of life and constitutes 9% of LAP cases in HIV infected individuals [18]. LAP is most common in the neck, followed by the axilla, reactive hyperplasia and atypical lymphocyte infiltration are the most common pathology, and tuberculosis and lymphoma are the main causes of LAP [20]. In the current study, F18-FDG PET/CT was performed on nine patients with suspicion of malignancy. The lymph nodes were thought to be reactive in F18-FDG PET/CT in two patients, a biopsy was not performed, and it was decided to follow up these patients. Five of the seven patients who underwent biopsy were diagnosed with malignancy, and HIV-associated LAP was detected in two patients.

Mhlanga et al. analyzed the F18-FDG PET/CT scans of 41 HIV-positive patients and suggested that together with the analysis of quantitative PET metabolic parameters, it is a valuable tool for the differentiation of benign adenopathy from lymphoma [19]. In another study, thirteen patients with HIV-infected Burkitt lymphoma were retrospectively examined and it was determined that 54% of the patients had F18-FDG uptake associated with HIV LAP [21]. Tatar et al. reported higher SUVmax values in lymphomas than in infectious or reactive nodes [22]. In the current study, there were no F18-FDG PET/CT imaging findings suggestive of malignancy in two patients. Considering malignancy in seven patients, biopsy was performed and malignancy was diagnosed in four of these patients and HIV-related LAP was diagnosed in two. According to these results, the high SUVmax of the lymph nodes of lymphoma makes it possible to distinguish between HIV-related infections and HIV-related generalized LAP.

The current ARTs used in the treatment of cases diagnosed with malignancy are less toxic and more reliable drugs than in the past. Somay et al., conducted a study to determine the ART-related follow-up results of patients receiving chemotherapy. During a 3-year follow-up period, the use of ART in combination with chemotherapy regimens led to better therapeutic outcomes and no mortality was observed [23]. However, one of the current study patients who received chemotherapy died during follow-up despite receiving ART. Follow-up and treatment are continuing for two of the patients in this study. As studies to date have included low numbers of patients, there is a clear need for further large-scale studies.

The mortality rate from AIDS-defining cancers decreases, but Non-Hodgkin lymphoma remains the most common cause of death due to cancer. The incidence of Non-Hodgkin Lymphoma has decreased in people with AIDS and survival has increased in the ART era, but patients still die from AIDS-related Non-Hodgkin Lymphoma [24]. In the current study, the most frequently detected HIV-related cancers were Kaposi's sarcoma and Non-Hodgkin lymphoma. Non-Hodgkin lymphoma was detected in one patient, who was newly diagnosed with HIV, but this patient died during follow-up.

Yin et al. mentioned that F18-FDG PET/CT showed involvement of multiple lymph node in -HIV-related Kaposi's sarcoma [25]. In another study by Tatar et al., Kaposi's sarcoma was characterized by multifocal widespread

lesions with different distribution, involving the nose, mouth, larynx and gastric mucosa, as well as cutaneous/subcutaneous nodules [22]. In the current study, F18-FDG PET/CT was performed to enable the detection of a primary tumor after cervical and mediastinal LAPs were seen on neck and thorax CT scans. Bilateral cervical and bilateral obturator, external iliac and inguinal LAPs were determined on PET/CT. The final diagnosis was Kaposi's sarcoma after the cervical lymph node biopsy. These studies demonstrated that F18-FDG PET/CT in HIV-positive patients was useful in identifying occult lesions in systemic Kaposi's sarcoma, which are difficult to identify with conventional imaging methods.

Since the introduction of ARTs, lung cancer has been the most common non-AIDS-defining cancer in AIDS patients who died. People infected with HIV who are also heavy smokers have an increased risk of lung cancer [26,27], and other factors such as frequent lung inflammation or infections contribute to the synergy with tobacco [28]. In the current study, one patient with lung malignancy died during follow-up.

Tatar et al. reported that the SUVmax values of HIV-related reactive LAP, HIV-related infections and HIV-related malignancy were not statistically significant with a SUVmax of 23.8 in lymphoma, 8.7 in Kaposi's sarcoma, 15.2 in tuberculosis, and 10.5 in benign LAP. However, the pattern of nodal or extranodal hypermetabolism may help in the differentiation of these conditions [22]. It has been previously reported that when the cut-off point of SUVmax of the lymph nodes was accepted as 8.0, specificity was 89.2% and sensitivity was 63.6% in the discrimination of malignant lymphoma and inflammatory LAP [29]. In the current study, the SUVmax of the LAP in two patients with HIV associated LAP were 6.40 and 5.05, whereas the SUVmax value of LAP was 8.56 in the patient with Hodgkin lymphoma and 8.25 in Kaposi's sarcoma. The SUVmax of the LAP in Non-Hodgkin lymphoma was very high with a value of 27.71. If the cut-off point of SUVmax is accepted 8.0, as in the study of Chen et al, patients can be discriminated as malignant or benign [29]. However, these results cannot be compared due to the low number of patients.

Limitations

Limitations of this study can be the retrospective design, with regional data, and a low number of cases.

Conclusion

F18-FDG PET/CT may significantly assist in the management of LAP in individuals with HIV. It has been predicted that as the survival rate in HIV-positive individuals increases, cancer cases will also increase. Non-HIV-related malignancies are becoming more common. Kaposi's sarcoma and Non-Hodgkin Lymphoma are AIDS-defined malignancies that are more common in HIV-positive patients and were also detected in this study. PET/CT imaging can demonstrate the distribution of HIV-associated LAPs and identify the area where the biopsy should be performed. The use of F18-FDG PET/CT can be considered preferable in the evaluation of HIV-related malignancies.

Ethical approval

Ethical approval was obtained for this study from the Hatay Mustafa Kemal University Non-Interventional Clinical Research Ethics Committee (date: 07.06.2023, decisions number: 15).

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