Global Health & Medicine. 2019; 1(1):49-54. ORIGINAL ARTICLE

DOI: 10.35772/ghm.2019.01015

# Non-AIDS-defining malignancies in Japanese hemophiliacs with HIV-1 infection

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**Abstract:** Along improvement of prognosis of HIV-1-infected patients due to successful anti-retroviral therapy, main causes of death in the patients have been changing from AIDS to non-AIDS defining malignancies (NADM) recently. However, little is known about the prevalence and incidence of NADM in patients, and especially in HIV-1-infected hemophiliacs. We prospectively conducted NADM screening with FDG-PET, chest CT, upper gastrointestinal endoscopy, tumor markers, and stool occult blood in hemophiliacs with a mean age of 48.9 years. Screening was done twice from December 2016 through March 2019; the first screening was used to calculate prevalence in 69 patients and the second was used to calculate incidence in 56 patients. The first screening revealed 4 cases of malignancies; three were cases of thyroid cancer and one was a case of a neuroendocrine tumor in the pancreas; prevalence was 5.8% (95% CI: 0.2-11.4%). During a mean follow-up of 1.2 years with 68.2 person-years (PYs), cancer was diagnosed in 2 cases (pancreatic and liver cancer) during the second screening. Incidence was 2.99/100 PY. It can be speculated that there might be around 40 cases of undiagnosed NADM currently and 20 cases of new NADM annually in this population, because 718 HIV-1-infected hemophiliacs are surviving in Japan according to the 2018 Nationwide Survey on Coagulation Disorders. Screening for NADM in HIV-1-infected hemophiliacs at other hospitals is strongly recommended.

***Keywords*:** Cancer, screening, prevalence, incidence

## Introduction

The prognosis for HIV-1-infected patients improved drastically thanks to continuous advances in antiretroviral therapy (ART), the life expectancy of those patients was estimated to be almost the same as that of the general population, especially after 2000 (*1-4*). Along with that improvement, HIV-1-infected patients now face issues related to aging. Some patients need to be treated for lifestyle-related co-morbidities such as hypertension, chronic kidney diseases, cardiovascular diseases, and diabetes mellitus (*5*). In addition to these co-morbidities, HIV-associated neurocognitive disorders (HAND) have been recognized as a major issue for patients in this decade (*6*). We performed the Japanese nationwide study of HAND (the J-HAND study), which revealed 25% of HIV-1-infected patients were diagnosed as HAND, though hemophiliacs were not included in that study (*7*). Moreover, the risk of non-AIDS-defining malignancies (NADM) has been increasing (*8-10*), and NADM have become one of the major causes of death in HIV-infected patients (*11*).

In Japan, around 30% of all hemophiliacs were infected with HIV-1 through contaminated blood products produced in the US before 1986 (*12*), when use of non-heat-treated products was prohibited in Japan. The number of HIV-1-infected hemophiliacs was 1,439 at that time. ART was introduced in Japan at the end of 1996, and the prognosis for hemophiliacs improved to that of other HIV-1-infected patients (*13*). However, nearly 99% of Japanese hemophiliacs were also infected with hepatitis C virus (HCV). Disease progression of hepatitis C in HIV-1 co-infected patients was reported to be more advanced than that in HCV mono-infected patients (*14*). Indeed, hepatitis C status has already advanced to cirrhosis in almost half of hemophiliacs (*15*). Therefore, hepatitis C has been

extensively treated with interferon and/or direct-acting antiviral drugs (DAA) for two decades, and a sustained virological response (SVR) has been achieved in almost all HIV-1-infected hemophiliacs (*16*). Although the risk of hepatocellular carcinoma (HCC) can be reduced after SVR with DAA (*17*), there is still a substantial risk of HCC, and especially in patients with cirrhosis. In summary, HIV-1-infected Japanese hemophiliacs have unique characteristics: *i*) they were infected with HIV-1 more than 33 years ago, *ii*) they were also co-infected with HCV, although they obtained SVR, *iii*) they had a long history of treatment with nucleoside reverse transcriptase inhibitors (NRTI), indicating that they might have received mitochondrial toxicities, *iv*) their mean age was 48.9 years, which is close to the age of cancer onset in HIV-1-infected patients (*10*), *v*) they were not received examination for HAND.

Therefore, it could be postulated that HIV-1-infected Japanese hemophiliacs might have a substantial risk of NADM. However, little is known about that risk in this population. The aims of the current study were to explore the prevalence and incidence of NADM and to conduct co-screening for HAND using 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET). This study focused only on NADM, and the HAND results in this population will be reported elsewhere.

## Patients and Methods

### *Patients*

A single center, prospective, longitudinal study of screening for NADM was conducted in HIV-1-infected Japanese hemophiliacs attending the AIDS Clinical Center (ACC), National Center for Global Health and Medicine (NCGM). All hemophiliacs were approached, and all eligible patients who agreed to participate in this study were included. Patients who were already diagnosed with an NADM were excluded in order to determine the undiagnosed prevalence of NADM.

Screening was conducted twice from December 2016 through March 2019. The first screening aimed to determine the prevalence of NADM and the second aimed to calculate its incidence in this population. In both screenings, patients underwent whole body FDG-PET, chest computed tomography (CT), gastric fibroscopy (GF), two tests for occult blood in stool, and measurement of tumor markers including carcinoembryonic antigen (CEA) for colon cancer, α-fetoprotein (AFP) for hepatocellular carcinoma, carbohydrate antigen (CA19-9) for biliary tract cancer or pancreatic cancer, pancreatic cancer-associated antigen (DUPAN-2) for pancreatic cancer, SPan-1 antigen (SPan-1) for pancreas and biliary tract cancer, prostate-specific antigen (PSA) for prostate cancer, cytokeratin 19 fragment (CYFRA) for non-small lung cancer, and pro-gastrin releasing peptide (ProGRP) for small cell lung cancer. If at least one of these examinations was positive, further specific examinations were added to identify or exclude NADM. This study was approved by the ethical committee at the NCGM (NCGM-G-2065-00), and all patients provided written informed consent in accordance with the Declaration of Helsinki. This study was registered with UMIN CTR (ID: UMIN000024741).

### *Statistical analysis*

Mean age ± standard deviation (SD), AIDS status, cirrhosis status, CD4 count, and plasma HIV viral load (pVL) were calculated at the time of the first screening. The prevalence of NADM was expressed with 95% confidential intervals (95% CI), and the incidence was calculated per 100 person-years (100 PYs).

## Results

### *Study participants*

A summary of the study participants is listed in Table 1. HIV-1-infected Japanese hemophiliacs were included while patients with von-Willebrand disease were not. Thus, all study participants were male. Among the 85 hemophiliacs seen by the ACC, 69 patients gave consent for the first screening and 58 for the second screening. The flow of this study is shown in Figure 1.

The mean age (± SD) of the 69 patients during the first screening was 48.9 ± 8.01 years, with the youngest age being 37 years and the oldest being 71 years.

**Table 1. Characteristics of 69 HIV-1-infeceted Japanese hemophiliacs during the first screening in 2016/2017**

| Characteristic | N (%) |
|---|---|
| Age, Years | |
| - 39 | 8 (11.6) |
| 40-49 | 33 (47.8) |
| 50-59 | 20 (29.0) |
| 60 - | 8 (11.6) |
| Mean ± SD[#1] | 48.9 ± 8.01 |
| History of AIDS-related illnesses | |
| Yes | 11 (15.9) |
| No | 58 (84.1) |
| Cirrhosis status | |
| Yes | 13 (18.8) |
| No | 56 (81.2) |
| CD4 count, cells/mm$^3$ | |
| < 200 | 2 (2.9) |
| 200-500 | 29 (42.0) |
| > 500 | 38 (55.1) |
| Mean ± SD | 575 ± 285 |
| Plasma viral load, copies/mL | |
| < 50 | 66 (95.7) |
| > 50 | 3 (55[#3]/57/44,400) [#2] |

[#1], standard deviation; [#2], plasma viral load of each patient; [#3]; elite controller.

All patients received ART except one who had never received any ART because he was an elite controller. His CD4 count was 703 cells/mm$^3$, and pVL was 55 copies/mL without ART. Although eleven patients (15.9%) had a history of AIDS-related illnesses, no patient had an active AIDS-defining illness during screening. Therefore, the mean CD4 count was 575 cells/mm$^3$, and pVL was below 50 copies/mL in 95.7% of patients. Overall, HIV-1 infection in this population was quite well controlled. Although an SVR had been achieved in all patients according to plasma HCV RNA, the hepatitis status had advanced to liver cirrhosis in 13 patients (18.8%), indicating there might have some risk of HCC in these patients.

*The first screening*

NADM was detected in 4 of 69 participants (Table 2). Therefore, the prevalence of NADM was 5.8% (95% CI: 0.2-11.4%). The NADM was thyroid cancer in three cases and a neuroendocrine tumor in one. All of the NADM were detected with FDG-PET and then examined further. Two cases of thyroid cancer were confirmed with an echography-guided biopsy.

When the first case of papillary thyroid cancer was diagnosed on November 22, 2017, the tumor was 10 × 10 × 7 mm in size and lymph node metastasis was present. The tumor was surgically resected. The stage of the cancer was pT1aN1aM0. The patient's CD4 count was 484 cells/mm$^3$, and pVL was undetectable. The second case of follicular thyroid cancer was diagnosed on January 9, 2018, and surgical resection was performed on May 17, 2018. The tumor was 17 mm in size and metastasis was absent; the stage of the cancer was pT1N0M0. The patient's CD4 count was 1058 cells/mm$^3$, and pVL was undetectable at that time. However, echography revealed metastasis to the right cervical lymph node on April 2, 2019 (11 months after the first surgery), and a second surgery was performed on June 3, 2019. In the third case (CD4, 429 cells/mm$^3$; pVL, undetectable), echography strongly suggested papillary carcinoma, but the patient refused further examinations. This case has been included here as a case of thyroid cancer. The fourth case (CD4, 530 cells/mm$^3$; pVL, 41copies/mL) was definitively diagnosed as a neuroendocrine tumor in the pancreas based on abdominal CT and MRI and by performing an endoscopic ultrasound (EUS) with fine needle aspiration. The patient in this case underwent successful surgical resection without any metastasis to or invasion of the surrounding tissue on February 1, 2018. The tumor was 16 × 15 × 14 mm size, and the stage of the cancer was pT1N0M0.

In the first screening, FDG-PET was a very sensitive way to identify NADM. However, there were false-positive results in 12 cases (18.8%). Those patients had to undergo further examinations to rule out NADM (Table 3). Lung cancer was most commonly (in four cases) suspected in FDG-PET and excluded by chest CT. Each of Colon cancer

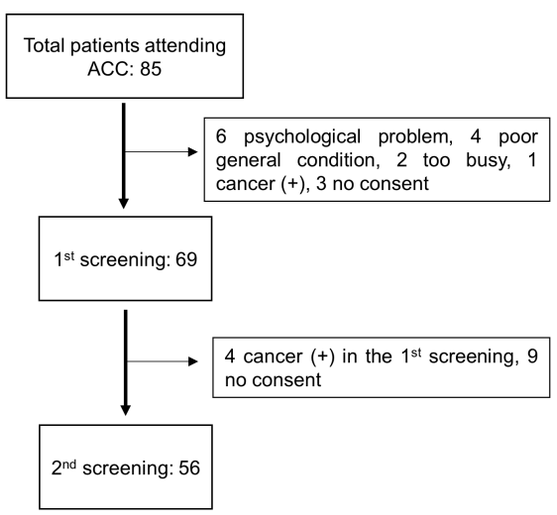


**Figure 1. Flow of this study.**

**Table 2. Diagnosis of NADM**

| NADM | Age, year | Modalities performed | Tumor marker |
|---|---|---|---|
| 1st screening | | | |
| 1. Thyroid ca (papillary ca) | 55 | PET, echo+biopsy | CYFRA; 4.0 ng/mL [#2] |
| 2. Thyroid ca (follicular ca) | 44 | PET, echo+biopsy | W.N.L |
| 3. Thyroid ca[#1] (s/o papillary ca) | 45 | PET, echo | W.N.L |
| 4. Neuroendocrine tumor, pancreas | 39 | PET, abd CT and MRI, EUS-FNA | W.N.L |
| 2nd screening | | | |
| 1. Pancreas ca (invasive ductal ca) | 69 | PET, abd CT and MRI, EUS | CYFRA; 5.1 ng/mL, DUPAN-2; 217 U/mL |
| 2. Hepatocellular ca (moderately differentiated) | 68 | PET, abd CT and EOB-MRI | DUPAN-2; 197 U/mL |

Abbreviations: ca, cancer/carcinoma; NADM, non-AIDS-defining malignancies; s/o, suspected of; PET, 18F-fluorodeoxyglucose-positron emission tomography; echo, echography; abd, abdominal; CT, computed tomography; EOB-MRI, Gd-ethoxybenzyl-DTPA-enhanced magnetic resonance imaging; EUS, endoscopic ultrasound; FNA, fine needle aspiration; CYFRA, cytokeratin 19 fragment (<3.5 ng/mL); DUPAN-2, pancreatic cancer-associated antigen (<150 U/mL); W.N.L, within normal limits for all tumor markers examined. [#1], A definitive diagnosis was not reached in this case because this patient refused further examinations. However, thyroid cancer was strongly suspected based on several imaging examinations that were performed. This case was included as a case of cancer. [#2], Repeated CYRFA results were within normal values, indicating non-specific elevation during the first examination.

**Table 3. False-positive results of FDG-PET in 12 cases**

| Case # | FDG uptake in | Suspected of | Further examinations |
|---|---|---|---|
| 1 | Rt lobe of thyroid | Thyroid ca | FNA under thyroid echo |
| 2 | Upper esophagus | Esophagus ca | GF, Chest CT |
| 3 | End ileum/Pancreas | Colon ca./Pancreas ca | GF, CF, abd CT, and echo |
| 4 | Rt lower lung | Lung ca | Chest CT |
| 5 | Pancreas | Pancreas ca | GF, MRCP |
| 6 | Rt lower lung S6 | Lung ca | Chest CT |
| 7 | Rt middle lung | Lung ca | Chest CT |
| 8 | Rt upper lung | Lung ca | Chest CT |
| 9 | Duodenum | Duodenum ca | GF |
| 10 | Ascending colon | Colon ca | CF |
| 11 | Liver S4 | Hepatocellular ca | Abd CT and EOB-MRI |
| 12 | Axillary lymph node | Metastasis ca | Abd echo and CT |

Abbreviations: ca, cancer/carcinoma; FDG-PET, 18F-fluorodeoxyglucose-positron emission tomography; FNA, fine needle aspiration; echo, echography; GF, gastric fibroscopy; CF, colon fibroscopy; abd, abdominal; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; EOB-MRI, Gd-ethoxybenzyl-DTPA-enhanced magnetic resonance imaging.

and pancreatic cancer was suspected in FDG-PET in two cases, respectively, but excluded by GF or colon fiberscope (CF), abdominal CT scan, or Magnetic resonance cholangiopancreatography (MRCP). Each of thyroid, esophagus, duodenum, hepatocellular, and metastatic cancer in axillary lymph node was suspected in one case, respectively, but excluded by further examinations. Tumor markers had no diagnostic value during the first screening.

*The second screening*

After a mean follow-up period of 1.2 years (67.2 PYs), cancer was diagnosed in 2 of the 56 study participants in the second screening, pancreatic cancer was diagnosed in one case and HCC was diagnosed in the other (Table 2). The incidence of NADM was 2.99/100 PYs in this population. Both of the aforementioned patients had already liver cirrhosis.

The patient with pancreatic cancer underwent the first screening with FDG-PET on January 26, 2017, and results were negative. The second screening was performed on May 31, 2018, revealing uptake of FDG in the pancreas. An abdominal CT was added on August 10, 2018, EUS was added on the August 20, and MRI was added on the August 21, resulted the strongly suspicion of pancreas cancer. In this case, however, a previous abdominal CT scan done on January 17, 2018 (4 months before the second FDG-PET) was negative for pancreatic cancer. The patient's CD4 count was 357 cells/mm$^3$, and pVL was undetectable during the second FDG-PET. The patient underwent surgical resection of pancreatic cancer on August 24$^{th}$. The cancer was pT2N0M0, stage IB. The pathological diagnosis was invasive ductal carcinoma. The patient with HCC underwent the first screening with FDG-PET on June 22, 2017, and results were negative. The second screening was performed on August 22, 2018, revealing uptake of FDG in the liver. The patient's CD4 count was 238 cells/mm$^3$, and pVL was undetectable during the second FDG-PET. An abdominal CT scan performed on June 22, 2018 (2 months before the second FDG-PET) was negative, but a scan on September 21$^{st}$ (1 month after the second one) strongly suggested HCC. HCC was confirmed radiologically with Gd-ethoxybenzyl-DTPA-enhanced MRI (EOB-MRI) on October 16$^{th}$, and the patient underwent surgical resection of HCC on October 25, 2018. The cancer was pT2N0M0, stage II. The pathological diagnosis was moderately differentiated HCC.

## Discussion

This is the first prospective longitudinal study of cancer screening in HIV-1-infeceted Japanese hemophiliacs. This study determined the prevalence and incidence of NADM in this population. In the light of the mean age of this study population (48.9 years), the prevalence (5.8%) and incidence (2.99/100PY) of NADM might be high (*9*). HIV infection was very well controlled in this population, and the mean CD4 count was 575 cells/mm$^3$. The CD4 count in patients who had an NADM during the first screening was higher than 400 cells/mm$^3$, suggesting that their immune function was sufficient to avoid opportunistic infections related to AIDS. However, the recovery of their immune system was not complete enough to mitigate the development of an NADM. The number of survivors among HIV-1-infected hemophiliacs was reported to be 718 patients as of March 2018 (*18*). Presumably there might be around the 40 cases of undiagnosed NADM currently and the 20 cases of new NADM annually in this population in Japan.

The methods of cancer screening in this study included whole body FDG-PET, chest CT, GF, measurement of tumor markers, and 2 tests for occult blood in stool because a retrospective study by the current authors found that gastric cancer, colon cancer,

lung cancer, and liver cancer were predominant forms of NADM (*9*). FDG-PET was used because FDG-PET is a very sensitive way to detect occult cancer (*19*) as well as dementia (*20*). Then, we aimed to make co-screening of NADM and HAND with FDG-PET in the original protocol. Since FDG-PET was used as a screening tool, the types of cancer detected in this study differed from those detected in the previous retrospective study (*9*). FDG-PET is reported to be highly sensitive at detecting colon/rectum, thyroid, and lung cancers but relatively less sensitive at detecting prostate and gastric cancers (*19*). In the current study, FDG-PET revealed three cases of incident thyroid cancer. There are some arguments that as the natural course of the thyroid cancer is very slow and the prognosis is not poor in most cases, then, finding the early stage thyroid cancer is not appropriate by using the sensitive method such as FDG-PET in general population (*21,22*). In HIV-1-infected patients, however, progression of some diseases, such as hepatitis C, is reported to be faster than that in the general population (*14*). Progression of thyroid cancer in HIV-1-infecetd patients is unclear and must be carefully followed in the future. In two of the current patients with thyroid cancer, the disease was relatively advanced, and patients had to undergo surgical resection. However, the cancer was found during the first screening, so disease progression in those cases was unclear. We should observe the third case with careful and close monitoring.

There are no guidelines regarding NADM screening in HIV-1-infected patients. Based on the current findings, NADM screening should be considered for those patients. However, the method of screening should be based on epidemiological data indicating how frequently NADM develop in HIV-1-infected patients (*9*). The current study used FDG-PET because this study sought to co-screen for dementia. However, FDG-PET is not inappropriate as a screening tool because FDG-PET yielded false-positive results in 12 cases; the patients in those cases had to undergo further examinations (including invasive procedures) to rule out an NADM (Table 3). Moreover, if it was listed, it is impossible to perform NADM screening in most of hospitals in Japan. We have a plan to conduct NADM screening again in the same population with chest and abdominal CT including the thyroid and prostate, GF, tests for occult blood in stool, and measurement of the tumor markers CEA, AFP, and PSA. This next screening would provide more accurate data on the incidence of NADM in HIV-1-infected hemophiliacs and indicate the usefulness of screening methods in the future.

This study had several limitations. First, this was a single-center study with a small number of patients, even though all patients seen by the ACC were approached and all eligible patients were included. There might be some institutional bias. Second, the mean observation period of 1.2 years was too short. The incidence certainly tended to be high, indicating the possible overestimation of NADM in this population. The current authors plan to address this issue by continuing to conduct cancer screening to obtain more accurate data. Third, this study did not include HIV-1-infected non-hemophiliacs or non-HIV-1-infected hemophiliacs who were age-matched to study participants, so the data on prevalence and incidence cannot be compared to data from other populations. Accordingly, whether data obtained in this study were specific to HIV-1-infected hemophiliacs or not it is unclear.

In conclusion, this study found that the prevalence and the incidence of NADM might be unexpectedly high in HIV-1-infected hemophiliacs under the mean age of 48.9 years, suggesting the NADM screening for this population in other hospitals should be strongly recommended.

**Acknowledgements**

This study was supported by a Grant-in-Aid for Research on AIDS from the Ministry of Health, Labor and Welfare of Japan (H28-AIDS-G-002). The authors wish to thank members of the Cancer Screening in Hemophiliac/HIV Patient Study Group that include the Outpatient Clinic of the ACC, NCGM; Junko Tanuma, Koji Watanabe, Takahiro Aoki, Daisuke Mizushima, Yasuaki Yanagawa, Ei Kinai, Haruka Uemura, Miwa Ogane, Pharmacy; Kazuhiko Nakajima, Jyoji Arakawa, Department of Radiology; Kiyoyuki Kodama, Hironori Kajiwara, Fumio Sunaoka, Hisayoshi Mizunuma, Yasutake Ishikawa, Daisuke Horikawa, Satoshi Ichino, Sayuri Kawajiri, Tomonori Arai, Syun Ostuka, Takumi Iwase, Daisuke Ishibashi, Toshiki Nosaka, Kiminari Nagai, and Tsubasa Sugihara. The authors also wish to thank Ms. Akiko Nakano for her logistic support of this study.

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Received July 31, 2019; Revised September 25, 2019; Accepted September 30, 2019.

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