Keywords: epidemiological study, HIV, leukemia, lymphoma, non-AIDS-defining hematological malignancy

Introduction

By the end of 2010, a total of 12 648 cases of HIV infection and 5799 cases of AIDS were reported in Japan [1]. The prevalence of HIV infection is estimated to be less than 0.1% [1]. However, the number of newly reported HIV-infected individuals has gradually increased, and the estimated number now ranges from 6300 to 10 000[1]. Most of the HIV-infected population in Japan is men [2]. The morbidity and incidence of infections has decreased as the introduction of highly active antiretroviral therapy (ART). The incidence of AIDS-defining malignancies has also decreased [3,4].

Although the incidence of AIDS-related non-Hodgkin's lymphoma (NHL) is decreasing, other hematological malignancies such as acute myeloid leukemia (AML), Hodgkin's lymphoma, and chronic myeloid leukemia (CML) are often reported. We conducted a nationwide epidemiological study to evaluate the incidence and clinical outcomes of non-AIDS-defining hematological malignancies (NADHMs), excluding NHL, in HIV-infected patients.

Methods

Most HIV-infected patients are followed in regional AIDS centers, and educational hospitals for hematologists cover most patients with hematological malignancies in Japan.

Questionnaires were sent to 429 regional AIDS centers, namely specialty clinical institutes for AIDS in each region certified by the Ministry of Health, Labor, and Welfare, and 497 educational hospitals certified by the Japanese Society of Hematology, namely training institutes for hematologists (207 of these institutions overlapped); in total, both the types of institutes will cover almost all the patients with HIV-related hematological malignancies in Japan. These institutes were requested to report all cases of hematological malignancies between 1991 and 2010, excluding NHL, in HIV-infected patients. We conducted a two-step inquiry. In the first step, all the institutes were required to answer the experience of NADHMs; if yes, the questionnaire was sent. The questionnaire included the date of diagnosis, subtype classification, chromosomal analysis, age, sex, CD4 count at the time of diagnosis, overall survival, treatment, response to treatment, date of relapse, and duration of ART.

Epidemiological data for HIV were acquired from the Joint United Nations program on HIV/AIDS (UNAIDS) [1]. The estimated size of the HIV-infected population in Japan was also based on the data from UNAIDS [1]. Data on AIDS and HIV estimates in Japan were available from 1990 to 2009. We calculated the crude incidence of NADHM from 1991 to 2009. Patient background and clinical data were analyzed using SPSS version 18.0 (IBM Japan, Inc., Tokyo, Japan).

Results

Responses were obtained from 511 institutes (response rate, 71.1%).

Patient characteristics

From 1991 to 2010, 47 patients with NADHMs were reported by 21 institutes, including 19 patients with Hodgkin's lymphoma, 13 with AML, seven with acute lymphoblastic leukemia (ALL), four with CML [three chronic phase (CML-CP) and one accelerated phase (CML-AP)], two with multiple myeloma, one with chronic lymphoid leukemia (CLL), and one with myelodysplastic syndrome–refractory anemia with excess blast one. The median age of the patients was 42.0 years (range, 21–70 years), with 93.6% being male. The median CD4-positive T-cell count was 255/μl (range, 1–1371/μl), and the median HIV viral load was 55 copies/ml. The median duration from the diagnosis of HIV infection to development of hematological malignancy was 28.0 months (range, 0–204 months) (Table 1). Prior to diagnosis, 68.1% patients were treated with ART (mean duration, 27.2 months) and 51.1% had AIDS. The median observation period after the diagnosis of NADHMs was 20.0 months (range, 0–140 months).

Subtypes of leukemia/lymphoma and cytogenetic abnormalities

Varying numbers of subtypes of AML were identified as follows: FAB-M1, M2, M3, M4, and M5. Four of the 13 patients with AML exhibited a normal karyotype; three exhibited recurrent cytogenetic abnormalities such as t(8;21), t(15;17), and inv(16);and three exhibited complex karyotypic abnormalities. Four of the seven patients with AML possessed Burkitt leukemia/lymphoma-type cytogenetic abnormalities such as t(8;14) or t(8;22). Three of the four patients with CML and 1patient with ALL possessed the Philadelphia (Ph^1) chromosome (Ph^1-ALL).

In 19 patients with Hodgkin's lymphoma, mixed-cellularity classical Hodgkin's lymphoma was the most common subtype (68%). Immunostaining revealed that 89% of the patients were positive for Epstein–Barr virus.

Table 1. Characteristics of patients with NADHMs.

		n (%)
Age	49.3 ± 12.9 (21–70) years	
Sex	Male	44 (93.6%)
	Female	3 (6.4)
Disease	Hodgkin's disease	19 (40.4)
	ALL	7 (14.9)
	AML	13 (27.7)
	MDS prior to AML	3 (6.4)
	MDS–RAEB	1 (2.1)
	CML	4 (8.5)
	CLL	1 (2.1)
	Myeloma	2 (4.3)
CD4/μl	Median 255 (1–1371)	
Time since HIV diagnosis	Median 28.0 (0–204) months	
AIDS prior to NADHMs		24 (51.1)
Prior ART		32 (68.1)
Duration of ART	Median 11.5 (0–108) months	

ALL, acute lymphoblastic lymphoma; AML, acute myeloid leukemia; ART, antiretroviral therapy; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NADHMs, non-AIDS-defining hematological malignancies; RAEB, refractory anemia with excess blast.

Treatments and outcomes

Most patients with AML and ALL received standard combination chemotherapy (such as cytarabine + daunorubicin and L-asparaginase + adriamycin, vincristine, prednisolone, cyclophosphamide), and the response rates for AML and ALL were 70.0 and 85.7%, respectively. However, the relapse rates for AML and ALL were 62.5 and 50%, respectively. The median overall survival (OS) period was 13 and 16 months for AML and ALL, respectively. The symptoms of three of the four patients with CML-CP were well controlled with imatinib. Four patients (2 AML, 1 Ph^1-ALL, and 1 CML-AP) were treated with allogeneic stem cell transplantation. One patient died because of acute graft-versus-host disease; however, three survived for more than 4 years. One patient with multiple myeloma was treated with autologous stem-cell transplantation without serious toxicity. Sixteen of the 19 patients with Hodgkin's lymphoma were treated with a combination of adriamycin, bleomycin, vinblastine, and dacarbazine or with radiation therapy. Eighty percent achieved complete remission. Details of treatments and outcomes of Hodgkin's lymphoma was described in another report [5].

Epidemiological analysis

There is an upward trend in the number of patients with NADHMs and the estimated number of HIV-infected patients [1] (Fig. 1). The estimated incidence of total NADHMs, Hodgkin's lymphoma, AML, ALL, and chronic leukemia (CLL, CML) was 32.6 (minimum–maximum, 27.2–41.3), 12.7(10.6–16.1), 8.0(6.6–10.1), 5.6 (4.6–7.1), and 4.0(3.3–5.0)/100 000 persons per year, respectively, between 1991 and 2009. The estimated crude incidence of total NADHMs increased 4.5-fold (4.3–5.4) from 1991–2000 to 2001–2009.

Discussion

The present study aimed to clarify the epidemiological status of NADHMs in Japan. Our results showed an estimated crude incidence rate of leukemia (CLL, CML, ALL and AML) of 17.6 (14.5–22.2)/100 000 persons per year in estimated HIV-infected individuals in Japan, which is 2.2-fold higher than that of leukemia (ICD10, C91–95) in the general population [6]. In addition, the estimated incidence of NADHMs has increased 4.5-fold (4.3–5.4) over the past decade.

The introduction of ART has improved the immunological status of HIV-infected individuals and reduced the incidence of AIDS-defining malignancies; however, the incidence of non-AIDS-defining malignancies is increasing. Several studies on non-AIDS-defining solid tumors suggest that aging; concomitant viral infection, such as that with Epstein–Barr virus, human papilloma virus, hepatitis C virus, and hepatitis B virus; low CD4 T-cell count with long-term immune suppression; and smoking are the possible causes of cancer [7–10]. However, the reason for the increased incidence of NADHMs remains unknown.

Recent developments in ART and supportive therapy for HIV-infected patients help facilitate long-term survival. Generally, aging is a key factor in carcinogenesis. In this study, we found that the mean age of patients with NADHMs was 49.3 years and that more than 30% were more than 60 years old, which is consistent with overall cancer trend.

Immune suppression is thought to be a risk factor for non-AIDS-defining malignancies. Krishnan *et al.* [9] analyzed prospective data of 3158 ART-naïve HIV-infected individuals and found that a recent low CD4 T-cell count is associated with non-AIDS-defining malignancies. In the present study, more than half of the patients with NADHMs had prior AIDS and their median CD4 T-cell count was less than 200/μl, suggesting that a low CD4 T-cell count is common in patients with NADHMs and may be one of the risk factors.

Uncontrolled HIV viral load is considered to be a risk factor for both AIDS-defining and non-AIDS-defining malignancies [11,12], and HIV itself may play a role in the onset of cancer. The regulatory proteins Tat and Vpr, which are encoded by the HIV genome, may contribute to oncogenesis [13,14]. However, a study by the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort showed no significant effect of viremiaon non-AIDS-defining malignancies [15]. In the present study, the HIV viral load was well controlled in more than 50% patients. Careful discussion is required to assess the association between carcinogenesis and HIV infection.

Before being diagnosed with NADHMs, the majority of patients were treated with ART, with the median

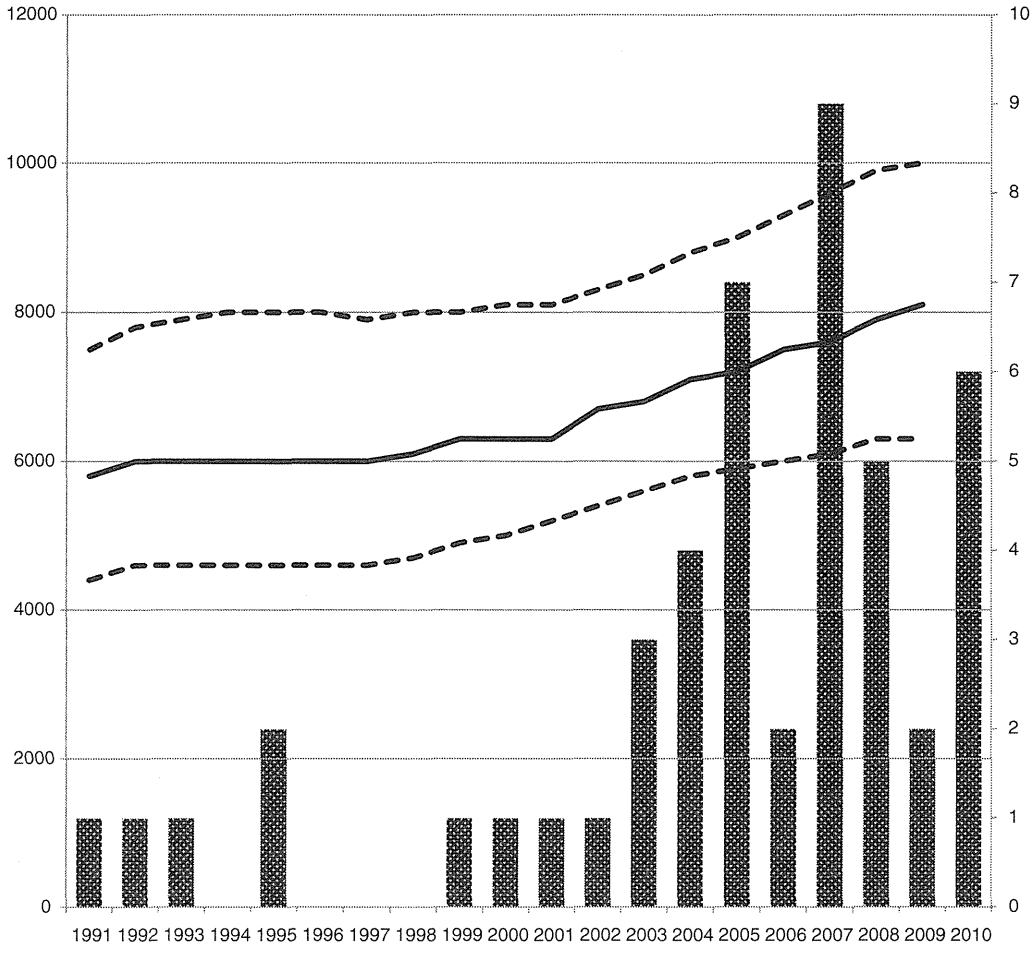

Fig. 1. The solid line shows the trend of the number of people in Japan estimated to be infected with HIV [1], and the dashed lines show the lower and upper ranges of the estimation. The solid bars indicate the number of patients with non-AIDS-defining hematological malignancies in each year.

duration of treatment being less than 1 year. Antiretroviral drugs can affect hematopoiesis, and zidovudine-containing regimens induce myelosuppression and possibly carcinogenesis [16]. Even when the duration of exposure to ART is short, its contribution to the development of NADHMs cannot be excluded.

We found that HIV-infected patients suffered from a variety of hematological malignancies, with a spectrum of NADHMs similar to that of HIV-negative patients. Cytogenetic analysis revealed typical chromosomal abnormalities of both acute and chronic leukemia. Moreover, adverse karyotypic abnormalities such as complex karyotype and/or monosomy, seven in AML and Burkitt-type karyotypes in ALL were often present. In three patients with AML with adverse karyotype, the duration of ART was more than 24 months. Long-term exposure to ART may cause therapy-related cytogenetic abnormalities.

In the present study, most patients with acute leukemia were treated with standard combination chemotherapy, and no deaths due to therapy were observed. Therapy appeared to be well tolerated, and the remission rate was similar to that of HIV-negative patients. In retrospective analysis, Sutton *et al.* [17] reported no deaths related to treatment of HIV-related AML in France, with a remission rate of 73.3%. Long-lasting remission of leukemia is rare in HIV-infected patients [18]. In the present study, more than 50% of the patients relapsed or represented primary refractory cases. However, two patients with AML and two with ALL continued in complete remission for more than 5 years. In the study by Sutton *et al.* [17], the estimated 5-year OS of 18 patients with AML was 19.9%, with a median survival period of 11 months [18]. There are several case reports of HIV-infected patients who have undergone stem-cell transplantation [19–21]. Five patients were found in our survey; however; only one death related to this therapy was observed. We conclude that stem-cell transplantation appears to be a feasible treatment for selected patients.

To summarize, a nationwide epidemiological study in Japan revealed that HIV-infected patients are at high risk for hematological malignancies, and the incidence of

these malignancies has increased in the past decade. The prognosis of HIV-infected patients was similar to that of HIV-negative patients. Standard chemotherapy may be a feasible treatment option for HIV-infected patients with hematological malignancies. Further study focusing on the mechanism of carcinogenesis in HIV-infected individuals is required.

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Conflicts of interest

The authors have no conflicts of interest.

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ORIGINAL ARTICLE

Clinical characteristics of human immunodeficiency virus-associated Hodgkin lymphoma patients in Japan

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Abstract The incidence of Hodgkin lymphoma (HL) is paradoxically increasing in the combination anti-retroviral therapy (cART) era. However, there has been no nationwide survey of human immunodeficiency virus (HIV)-associated HL (HIV-HL) in Japan. We retrospectively examined the clinical characteristics and outcomes of 19 newly diagnosed HIV-HL patients at 11 HIV/AIDS and hematology regional hospitals in Japan between 1991 and 2010. At the time of HL diagnosis, 79 % of patients were receiving cART. All the patients, but one received HL diagnoses in the cART era. The median CD4+ cell count at HIV-HL diagnosis was 169/μl. Mixed-cellularity classical Hodgkin lymphoma was the most common subtype occurring in 68 % of the patients; 89 % of the patients were positive for Epstein–Barr virus. Of these 19 patients, 84 % were in advanced stages, with bone marrow

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involvement observed in 47 % of the patients; 58 % had extranodal sites. All the treated patients were given cART concurrent with HL therapy. The complete remission rate of the treated patients was 87 %. The median OS of the entire cohort was 17 months. These results suggest that the characteristics of HIV-HL in Japan are more aggressive than those of non-HIV-associated HL in Japan, but standard chemotherapy is effective and feasible.

Keywords Hodgkin lymphoma · HIV infection · ABVD · Antiretroviral therapy · EBV

Introduction

The introduction of combination antiretroviral therapy (cART) has led to improvements in immune status among human immunodeficiency virus (HIV)-infected individuals, reducing acquired immune deficiency syndrome (AIDS)-related morbidity and prolonging survival. The incidence of non-Hodgkin lymphoma (NHL) and other AIDS-defining malignancies has declined substantially over the past 10 years. In contrast, the incidence of non-AIDS-defining malignancies including Hodgkin lymphoma (HL) does not appear to have decreased, and some studies have shown that its incidence may have increased [1–6].

The behavior of HIV-associated HL (HIV-HL) is known to be more aggressive than that of non-HIV-HL, with a higher frequency of poor prognostic features, such as an advanced stage, extranodal involvement, bone marrow involvement, B symptoms, with Epstein–Barr virus (EBV) positivity [7–9]. Several studies reported that the standard combination chemotherapy, such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and the Stanford V regimen in conjunction with cART were tolerable and effective in patients with HIV [9–11].

The number of HIV-1 infected individuals is continuously increasing in Japan, with increased prevalence of AIDS-related NHL [12]. Since the incidence of non-HIV-associated HL in Japan is approximately one-third of that in Western countries [13, 14], the incidence and features of HIV-HL in Japan need to be clarified. In this study, we performed a retrospective analysis to elucidate the specific features of HIV-HL in Japan.

Methods

We surveyed all 429 regional AIDS centers and all 497 educational hospitals certified by the Japanese Society of Hematology (207 of these institutions overlapped) and obtained data from 511 institutions (71.1 %). In this retrospective cohort study, we examined the clinical characteristics and outcomes of patients with diagnoses of HIV-HL who visited 11 regional hospitals for HIV/AIDS and/or hematological diseases in Japan between 1991 and 2010. This study was approved by the responsible Ethics Committee.

Patients

The patients included in this study had received new diagnoses of HIV-HL during the study period. The pathological diagnosis of each institution was accepted. All patients who satisfied the above-mentioned criteria were consecutively examined. Data from all examined patients were then statistically analyzed.

Clinical characteristics of the patients

Data regarding age, prior AIDS diagnosis, prior administration of antiretroviral therapy, CD4+ cell count at diagnosis, HIV viral load at diagnosis, and the performance status (PS) according to the criteria of the Eastern Cooperative Oncology Group (ECOG) at diagnosis were analyzed. Complete remission (CR) was defined as the disappearance of all clinical evidence of disease at the completion of the first induction therapy. The presence of residual disease, but with $\geq$50 % decrease in the sum of the product of the greatest diameter was defined as partial response (PR). Overall survival (OS) was defined as the interval from diagnosis to death from any cause. An International Prognostic Score (IPS) is defined as the number of adverse prognostic factors present at diagnosis, and predicts the rate of freedom from progression of disease [15].

Statistical analysis

Kaplan–Meier survival curves were used to evaluate OS. Data were statistically analyzed using Statcel2 for Excel 2007 (The Publisher OMS, Saitama, Japan).

Results

Baseline characteristics of the patients

Table 1 shows the baseline characteristics of the 19 patients with HIV-HL. The median age was 48 years (range 31–66 years), and 89 % of the patients were men. A total of 16 patients (84 %) were Japanese. Of the 19 patients, 10 had received a diagnosis of AIDS before the development of HIV-HL, and 15 (79 %) were receiving cART at diagnosis. All the patients except 1 received diagnoses of HL in the cART era (Fig. 1).

Table 1 Baseline characteristics at the time of Hodgkin lymphoma (HL) diagnosis

Men	17 (89 %)
Median Age, years (range)	48 (31–66)
Prior AIDS diagnosis	10 (53 %)
Absolute CD4 cell counts, cells × 10^9/l (range)	169 (1–567)
Viral load <500 copies/ml	11/17 (65 %)
ECOG PS, *n* (%)	
0–1	12 (63 %)
2	4 (21 %)
3–4	3 (16 %)
Histologic subtype *n* (%)	
Classical Hodgkin lymphoma	18 (95 %)
MCCHL	13 (68 %)
NSCHL	3 (16 %)
LDCHL	2 (11 %)
Non-specific	1 (5 %)
EBV positivity	16/18 (89 %)
Ann Arbor stage *n* (%)	
I	2 (11 %)
II	1 (5 %)
III	7 (37 %)
IV	9 (47 %)
B symptoms	11 (58 %)
Extranodal sites	11 (58 %)
Bone marrow involvement	9 (47 %)
IPS	
0–2	7 (37 %)
>3	12 (63 %)

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *MCCHL* mixed-cellularity classical Hodgkin lymphoma, *NSCHL* nodular sclerosis classical Hodgkin lymphoma, *LDCHL* lymphocyte-depleted classical Hodgkin lymphoma, EBV Epstein–Barr virus, *IPS* International Prognostic Score

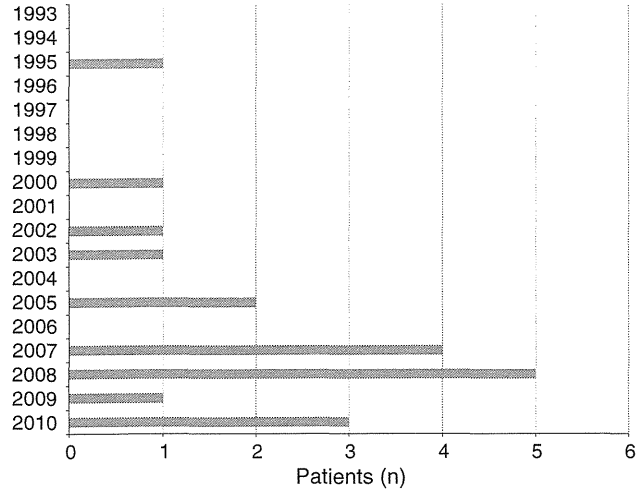

Fig. 1 Annual incidence of HIV-associated HL in Japan

The median CD4+ cell count at HIV-HL diagnosis was 169/μl (range 1–567/μl) and 1 patient with a CD4+ cell count of 1/μl had hemophagocytic syndrome at diagnosis. A total of 65 % of the patients had achieved an HIV viral load of <500 copies/ml at the diagnosis of HL, and 37 % of the patients had an ECOG PS of ≥2 at diagnosis. Mixed-cellularity classical Hodgkin lymphoma (MCCHL) was the most common subtype occurring in 13 (68 %) of the 19 HL patients, followed by nodular sclerosis classical Hodgkin lymphoma (NSCHL) occurring in 3 (16 %). A high frequency (89 %) of EBV association (EBER and/or LMP-1) was observed in HL tissues. A total of 84 % of the patients showed advanced stages (III, IV), with bone marrow involvement in 47 % of the patients. A total of 11 patients (58 %) had B symptoms and 11 patients (58 %) had extranodal sites. The number of patients with an International Prognostic Score (IPS) of 0–2, and the number of patients with an IPS of 3 or greater than 3 were 7 (37 %) and 12 (63 %), respectively.

Treatment and initial response

Of 3 patients who showed a localized stage, 2 were treated with ABVD therapy and radiotherapy and 1 was treated with radiotherapy alone. Among the patients who showed an advanced stage, 7 were treated with ABVD therapy. Of these 7 patients, 1 was not given bleomycin because of pre-existing interstitial pneumonia. Furthermore, 1 was given a reduced dose (/m^2 → /body) because of poor PS and pre-existing bone marrow suppression due to HIV infection without bone marrow infiltration of HL. A total of 6 patients were treated with ABVD therapy with a lower dose of dacarbazine (AVBd, 250 mg/m^2) and 3 patients could not be treated (2 patients received diagnoses at autopsy, and 1 with poor PS received a diagnosis during the pre-cART era). All the treated patients ($n = 16$) were given cART therapy concurrently with HL therapy.

Figure 2 shows the OS probabilities of the 19 patients. The median OS of the entire cohort was 17 months. The CR rate of the treated patients ($n = 15$) was 87 %: 1 patient achieved PR and 1 patient developed progressive disease (PD); 2 relapsed after achieving CR. The median progression-free survival (PFS) ($n = 19$) was also 17 months (Fig. 3).

Table 2 shows the status, CD4 cell counts and IPS of the patients. The 5-year survival rates of the patients with IPS of 0–2 and ≥3 were 86 % and 35, respectively ($n = 19$; $p = 0.095$ by logrank test) (Fig. 4). The CR rate of the advanced-stage patients who were treated with ABVD/ABVd therapy ($n = 12$) was 83 % (2 relapsed afterwards) and their survival rate ($n = 13$) was 56 % (Fig. 5). The survival rates of the advanced-stage patients treated with ABVD/ABVd ($n = 13$) with IPS of 0–2 and ≥3 were 75

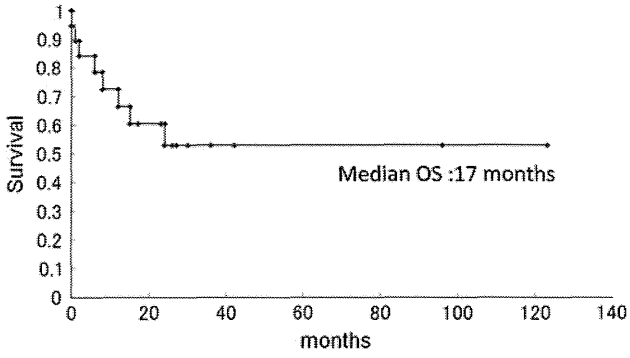

Fig. 2 Overall survival of the 19 patients

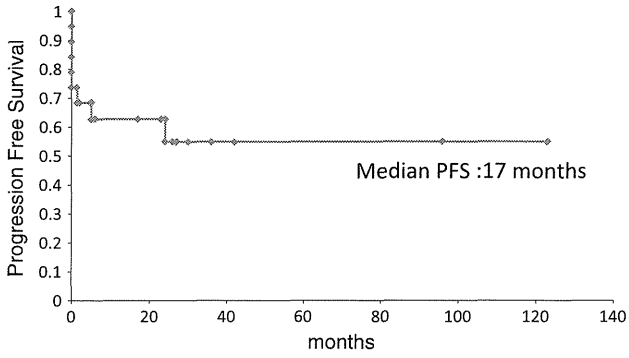

Fig. 3 Progression-free survival of the 19 patients

Table 2 Outcome, CD4 cell count and IPS of all patients

Patient No.	CD4 cell count	IPS	Survival (months)	Outcome
1	379	1	6	Alive (CR)
2	130	4	24	Dead (CR)
3	384	2	36	Alive (CR)
4	341	1	30	Alive (CR)
5	75	4	8	Dead (no treatment)
6	535	1	17	Alive (CR)
7	124	3	96	Alive (CR)
8	74	4	23	Alive (CR)
9	567	2	27	Alive (CR)
10	23	2	2	Dead (PD)
11	24	4	0	Dead (no treatment)
12	409	2	123	Alive (CR)
13	179	3	6	Dead (PR)
14	293	4	15	Dead (relapse)
15	452	3	26	Alive (CR)
16	1	4	12	Dead (relapse)
17	169	3	2	Alive (receiving treatment)
18	146	4	42	Alive (CR)
19	24	5	1	Dead (no treatment)

IPS International Prognostic Score, *CR* complete response, *PR* partial response

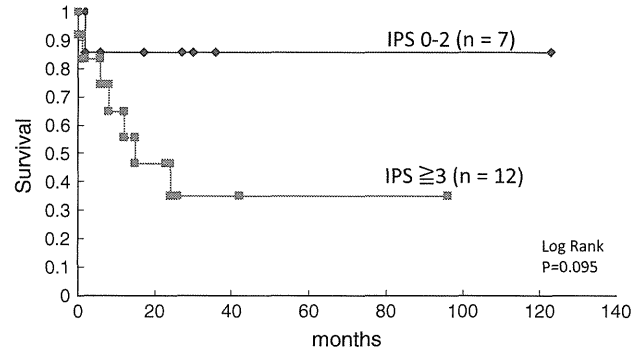

Fig. 4 Overall survival of the 19 patients according to IPS

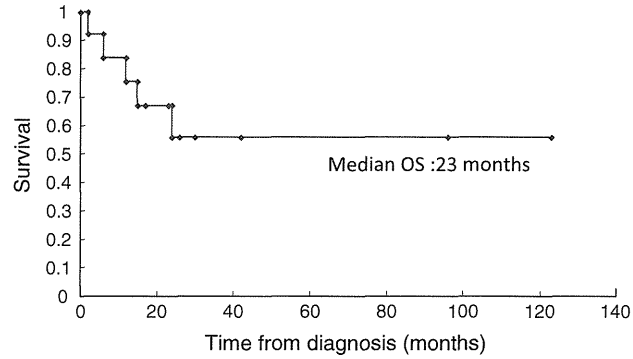

Fig. 5 Overall survival of the advanced-stage patients treated with ABVD/ABVd ($n = 13$)

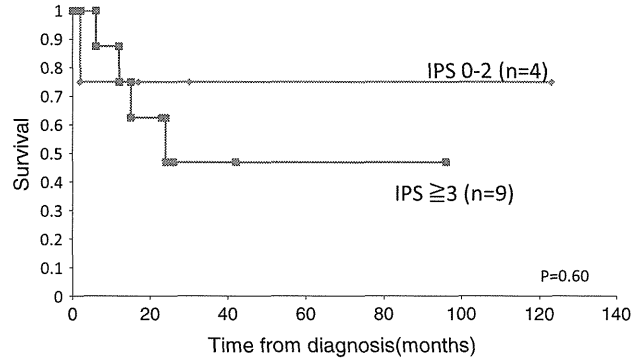

Fig. 6 Overall survival of the advanced-stage patients treated with ABVD/ABVd ($n = 13$) according to IPS

and 47 %, respectively (Fig. 6; $p = 0.60$ by logrank test). Of the 8 patients who died, the cause of death in 7 was HL (no treatment, $n = 3$; PR, $n = 1$; PD, $n = 1$; relapse, $n = 2$) and 1 patient died of infection and gastrointestinal perforation after the completion of therapy while in CR. The duration of grade 4 neutropenia was 0–12 days (median 7 days). With regard to bone marrow suppression, ABVD/ABVd was tolerable and no treatment-related deaths occurred during therapy. We were not able to assess the incidence of opportunistic infections.

Discussion

Although HL is not an AIDS-defining malignancy, its incidence is approximately 10 times higher in HIV-positive populations than in HIV-negative populations [16]. While the incidence of many opportunistic infections and some malignancies such as Kaposi sarcoma and NHL has been decreasing since the development of cART [1, 17], the incidence of HIV-HL has been increasing even in the cART era [2–5]. Recent data from the United States show that the estimated numbers of AIDS-defining cancers decreased by greater than threefold from 1991 to 1995 and from 2001 to 2005, whereas those of non-AIDS-defining cancers increased approximately threefold during the same periods and that of HL increased twofold [6]. The incidence of HIV-HL in Japan has also been increasing in the cART era after the year of 1996, based on the findings of the present study in which HL developed in all cases except 1 (Fig. 1).

In the present study, cART had been initiated in 79 % of the patients before the development of HL. A total of 65 % of the patients had achieved a viral load of <500 copies/ml at HL diagnosis. The suppression of RNA load and the presence of a higher CD4+ cell count did not appear to be useful to prevent the development of HL in the current series. Biggar et al. [3] showed that the incidence of HL after AIDS onset was higher in the cART era and in patients with a higher CD4 cell count. They suggested that the development of HL requires an inflammatory background which is absent in those with severe immunosuppression. Lanoy et al. [18] recently reported that HL risk was particularly elevated in months 1–3 of cART therapy, which suggests that immune reconstitution may play a role in some cases. HL developed in only 1 patient in months 1–3 in the current series of patients. A detailed physical examination of superficial lymph nodes even in patients with a good virological response condition is essential for an early diagnosis of HIV-HL.

HIV-HL is reported to be more malignant than non-HIV-HL [19]. HIV-HL is characterized by a high incidence of unfavorable histological subtypes such as MCCHL and lymphocyte-depleted classical Hodgkin lymphoma [3]. Our survey also revealed MCCHL to be the most common HL subtype in Japanese HIV-HL patients, whereas NSCHL is the most common subtype in Japanese non-HIV-HL patients according to 2 previous reports [20, 21]. A high frequency of EBV association (80–100 %) has been shown in the HL tissue of HIV-HL patients [3, 19, 22, 23], and LMP-1 is expressed in virtually all HIV-HL cases which support an etiologic role of EBV in the pathogenesis of HIV-HL, in contrast to an EBV-association incidence of only 20–50 % in non-HIV-HL [24, 25]. In the current series, 89 % of the patients with HIV-HL showed EBV positivity, similar to that of previous reports. It has been reported that the prevalence of EBV in Hodgkin and Reed-Sternberg cells varies according to the histological subtype and epidemiologic factors. The highest frequency (75 %) is found in MCCHL and the lowest (10–40 %) in NSCHL [26]. This may account for the finding that EBV positivity was high in HIV-HL patients in the present series. Previously, a decrease in the incidence of EBV-positive AIDS-related lymphoma from 88 % in the pre-cART era to 58 % in the cART era has been reported in Japan [27]. The major histological subtype was diffuse large B-cell lymphoma (DLBCL) and only 3.5 % of these patients had HL. In the current series, HL developed in only 1 patient in the pre-cART era, making a comparison difficult. However, high EBV positivity, even in the cART era, appears to be a marked characteristic of HIV-HL compared with DLBCL. However, it is still unclear why EBV-positive HIV-HL develops in well-controlled HIV-1 patients.

In non-HIV-HL patients, primary extranodal involvement is rare. More than 60 % of patients have localized disease (Stages I and II). Bone marrow involvement has been reported in only 5 % of cases [28]. The frequency of an advanced stage at HL diagnosis is high in patients with HIV, similar to that observed in patients with AIDS-related NHL. In the present study, 84 % of the patients were in an advanced stage. A high frequency of B symptoms (70–100 %), the presence of extranodal sites (30 %) and bone marrow involvement (40–50 %) have been reported in HIV-HL [29, 30]. The incidence rates of B symptoms, extranodal sites and bone marrow involvement were 58, 58, and 47 %, respectively, in the current series which is consistent with previous reports. The characteristics of HIV-HL in Japan were found to differ from those of non-HIV-HL in Japan, but similar to those of HIV-HL in other countries.

The prognosis of HIV-HL was poor in the pre-cART era. The AIDS Clinical Trial Group (ACTG) reported that in a prospective study of 21 HIV-HL patients treated with standard ABVD therapy without antiretroviral therapy (ART), the median survival was only 1.5 years. Despite the routine use of granulocyte colony-stimulating factor, opportunistic infections occurred in 29 % of the patients during and shortly after the study [30]. The ACTG reported the results of a phase II study of 21 patients (Stages III–IV patients, 81 %) treated with ABVD therapy without cART in which the CR rate was 43 % and the median survival was 18 months [31]. Little et al. [32] reported that cART administration during or at the end of systemic chemotherapy for HIV-associated lymphoma could prolong patient survival. A previous study of 62 retrospectively analyzed advanced-stage HIV-HL patients in Spain who were treated with ABVD concomitantly with cART reported a CR rate of 87 % and a 5-year OS of 76 % [4].

Prognosis has thus improved in the cART era, and patients can be treated similarly as immunocompetent patients.

The median OS of the entire cohort in our study ($n = 19$) was 17 months, and no treatment-related deaths were noted. The cause of death ($n = 8$) was HL in 88 % of the patients. Disease control, rather than infection control was more difficult in patients in our study which reflected the aggressive nature of HIV-HL. The contribution of EBV infection to the development of HIV-HL is still unknown. Keegan et al. have reviewed the association of EBV infection in non-HIV-HL patients, and found different types of association (i.e., worse prognosis, no association or better prognosis) [33]. These results suggest that the poorer prognosis of HIV-HL is not due to the presence of EBV. However, more cases are required to further clarify the contribution of EBV infection to the development of HIV+ HL.

ABVd therapy with a low dose of dacarbazine (250 mg/m^2) has been used for Japanese patients with advanced non-HIV-HL to prevent severe adverse effects, and has shown to be effective for Japanese patients with non-HIV-HL [21]. In the current series of patients, the CR rate of the advanced-stage patients who were treated with ABVD/ABVd ($n = 12$: ABVD, $n = 6$; ABVd, $n = 6$) was 83 %, and the 5-year survival rate ($n = 13$) was 56 %, which was inferior to that described in a previous report from Spain [4]. Further prospective studies are needed to evaluate the efficacy of AVBd therapy for Japanese HIV-HL patients.

IPS, defined as the number of adverse prognostic factors present at diagnosis, predicts the rate of freedom from progression of disease in patients with non-HIV-HL [15, 34]. Spina et al. [35] reported that a high IPS is also predictive of a worse outcome for patients with HIV-HL. In the current series of patients, the 5-year OS of patients with an IPS of 0 to 2 and ≥ 3 were 86 and 35 %, respectively ($n = 19$). Although it is not significant, a high IPS tends to result in lower survival rate. A randomized trial of aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous hematopoietic stem-cell transplantation (HSCT) for relapsed chemosensitive non-HIV-HL patients showed significantly better freedom from treatment failure for patients given HSCT [36]. High-dose chemotherapy and autologous stem-cell transplantation (ASCT) in the salvage setting of AIDS-related lymphoma (ARL) including HL have been demonstrated to be feasible [37] and have shown good tolerability and favorable disease-free survival and OS [38].

In conclusion, we conducted a nationwide survey of HIV-HL patients in Japan. We found that the incidence of HIV-HL in Japan is increasing, and that most of the patients with HIV-HL in Japan showed an advanced stage. Because the number of HIV-1-infected individuals receiving cART in Japan is expected to increase, clinicians who specialize in HIV infection need to be careful in the diagnosis of HIV-HL.

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CURRENT TOPICS

エイズ関連リンパ腫の病理診断

大田泰徳[*1] 比島恒和[*2] 望月 眞[*3] 児玉良典[*4] 片野晴隆[*5]

はじめに

日本におけるヒト免疫不全ウイルス human immunodeficiency virus (HIV) 感染者数は年々増加傾向にあり，2010年には年間1,075件の新規HIV感染者が報告されている[1]．新規HIV感染者の約7割が同性間の性的接触による感染であり，男性同性愛者の間でHIV感染が広がっている．悪性リンパ腫はエイズの合併症の中でも，予後が悪く，最も深刻なものの一つである．日本でも1997年頃から導入された抗レトロウイルス剤のカクテル療法 (highly active antiretroviral therapy：HAART) は患者の体内でのHIVの複製を効率的に抑え，現在ではHIV感染症も慢性疾患として扱うことができるようになってきた．HAARTが導入されてから，日和見感染症の発症頻度は減少傾向にあるが，リンパ腫やKaposi肉腫といったエイズ関連悪性腫瘍の発症率は，むしろ増加傾向にある[2]．現在では，エイズ患者の約5%程度がリンパ腫を合併しており，この発症頻度は2000年頃に比べると3倍程度になっている．

HAART導入後，エイズ関連リンパ腫の病態も変わりつつある．HAART導入前は，日本におけるエイズ関連リンパ腫のほとんどはEpstein-Barr virus (EBV) による日和見リンパ腫であり，組織型はdiffuse large B-cell lymphoma (DLBCL) であった[3]．しかし，近年はDLBCLに加え，Burkittリンパ腫 (BL) やHodgkinリンパ腫 (HL) がみられるようになり，さらには，primary effusion lymphoma (PEL) など，ほとんどHIV感染症にしか発症しないようなリンパ腫も日本で目にするようになった．エイズ関連リンパ腫では，いずれの組織型にしても，非典型像を示すことが少なくない．特に，臨床病理として苦慮するのはHIV感染者にはBLともDLBCLともとれない症例が多いことである．こうした，エイズ関連リンパ腫の特殊性と病理診断の難しさは多くのエイズ拠点病院の病理医が経験するところであり，WHO分類など，海外の成書の記載には判然としないものを感じていた．一方，臨床側からもエイズ関連リンパ腫の病理診断に関し，組織学的診断と臨床側の印象が異なる症例が少なくないとの意見が厚生労働科学研究費エイズ対策研究事業のエイズ関連リンパ腫研究班に寄せられていた．そこで，当該研究班の一事業として，東京および大阪の5つのエイズ拠点病院から，診断に苦慮した症例，珍しい症例など約40例を持ち寄り，複数施設の病理医が供覧する症例検討会を行った．検討した症例は，BLとDLBCLの鑑別が問題となった24例，human herpesvirus-8 (HHV-8) 関連リンパ腫5例，plasmablastic lymphoma 4例，Hodgkinリンパ腫，多発性骨髄腫，PTCL (peripheral T-cell lymphoma) が1例などである．検討の結果はエイズ関連リンパ腫の診断の困難さが浮き彫りになるものであり，同時に，診断に対するごく大まかなコンセンサスが得られたと参加者は感じた．

本稿は，WHO分類 第4版を基にエイズ関連リンパ腫の診断の要点を整理するとともに，日本のエイズ関連リンパ腫の診断に関して，その症例検討会に参加した病理医により，ある程度のコンセンサスが得られた意見を踏まえ，エイズ関連リンパ腫の診断を解説するものである．本稿の内容が，日本のエイズ関連リンパ腫の診断に多少なりとも有用な情報になれば幸甚である．

Ⅰ．エイズ関連リンパ腫の組織型

エイズ患者に合併するリンパ腫として，WHO分類で挙げられているものを**表1**に列挙した[4]．エイズ関連リンパ腫は一般的にはB細胞性であり，T/NK細胞

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表1　エイズ患者にみられるリンパ腫

疾患名	エイズ関連リンパ腫における頻度
・Burkitt lymphoma	3割程度
・Diffuse large B-cell lymphoma (DLBCL), not otherwise specified	Centroblastic variantが25～30%，immunoblastic variantが10%程度
・Hodgkin lymphoma	数%
・Primary effusion lymphoma ・Large B-cell lymphoma arising in HHV8-associated MCD ・Plasmablastic lymphoma	HIV陽性患者に特異的にみられるリンパ腫で，頻度は低い
・MALT lymphoma ・Peripheral T and NK cell lymphoma ・Polymorphic lymphoid proliferations resembling PTLD	エイズ関連リンパ腫では稀

リンパ腫の発症は稀である．また，**表1**以外のリンパ腫の発症も稀で，ほとんどの症例はここに挙げたもののどれかにあてはまる．2005年までにみられた日本のエイズ関連リンパ腫における組織型はDLBCLが78%，BLが7%であり，他の組織型の頻度は低いと考えられていた[3]．しかし，この統計はWHO分類 第4版が出版される前のものであり，DLBCLに分類されたものの中には現在の分類ではBLとすべき症例が多く含まれていると考えられる．欧米のエイズ関連リンパ腫ではBLが約3割と，最も頻度が高い．次にDLBCL, centroblastic variantが25～30%，DLBCL, immunoblastic variantが10%程度であり，他の亜型は数%程度である．日本のエイズ関連リンパ腫でも，近年EBV陽性のDLBCL, immunoblastic variantが減少し，BLが増加傾向にある，脳原発リンパ腫が減少しているなど，欧米の統計に近づいている印象がある（望月ら：日本病理学会誌 2010, 99：277．比島ら：日本病理学会誌 2011, 100：416）[3]．また，男性同性愛のエイズ患者の増加に伴い，HHV-8（KSHV）関連リンパ腫が増加しつつあることも大きな特徴である．以下，それぞれのリンパ腫の一般論と，今回検討した日本のエイズ関連リンパ腫における特徴を述べる．

1. Burkitt lymphoma (BL)

BLは古典的にはアフリカの小児に発生する極めて進行の速いB細胞性リンパ腫で，ほぼ100%の症例でEBVの関与があり，*myc*遺伝子を含む転座が非常に高率にみられる[5]．日本や欧米では小児のみならず高齢者にも発生し，EBVの陽性率は30%程度である．組織学的には中型リンパ球からなり，核クロマチンは繊細で核小体は小型でそれほど目立たない．腫瘍細胞はmonotonousでお互いに押し合うように密に増生している．核分裂像や核破砕物がみられ，核破砕物を貪食した組織球が混ざるstarry sky像を呈する．免疫組織化学的にはCD19，CD20陽性のB細胞性リンパ腫であり，CD10，BCL6等の胚中心型マーカーが陽性となる．BCL2は通常陰性となる．遺伝子学的には大半の症例で*myc*遺伝子に免疫グロブリン遺伝子との転座が起こっている．一般的に腫瘍細胞に対する治療反応性はよい．

エイズ関連リンパ腫の亜型としてのBLはWHO分類によるとエイズ関連リンパ腫の30%を占める[4]．約1/3の症例は通常のBLと同様の形態を示し，EBVの陽性率は30%であるが，残りの2/3の症例にはplasmacytoid differentiationがみられ，これはエイズ関連BLに特徴的である．plasmacytoid differentiationを伴うBLのリンパ腫細胞は，塩基性色素に富んだ豊富な細胞質に偏在した核をもつ，中程度の大きさの細胞が中心で，しばしば明瞭な核小体が核の中心にみえる．こうした細胞ではEBVは50～70%陽性である．

日本人のエイズ関連リンパ腫症例では典型的な組織像をとるBLはむしろ少数である．免疫染色ではCD20+，CD10+，BCL6+，BCL2−の典型的なBLのパターンをとり，*myc*遺伝子の異常も認められるが，細胞がより大型で多形性に富む例が多く，しばしばstarry skyパターンも欠いている（**図1**）．しかし，今回の検討結果からは，こうした形態学的にDLBCLの可能性も考慮すべき症例でも，免疫染色や*myc*遺伝子の検索で，BLのパターンをとる症例はBLと診断したほうが，より臨床的経過と合致した．このことは世界的にみられている傾向のようであり，旧分類でatypical Burkittに分類されるであろう，これらの症例は現在ではBLの範疇に含める．なお，日本のエイズ関連BLではplasmacytoid differentiationを伴う症例は多くない．

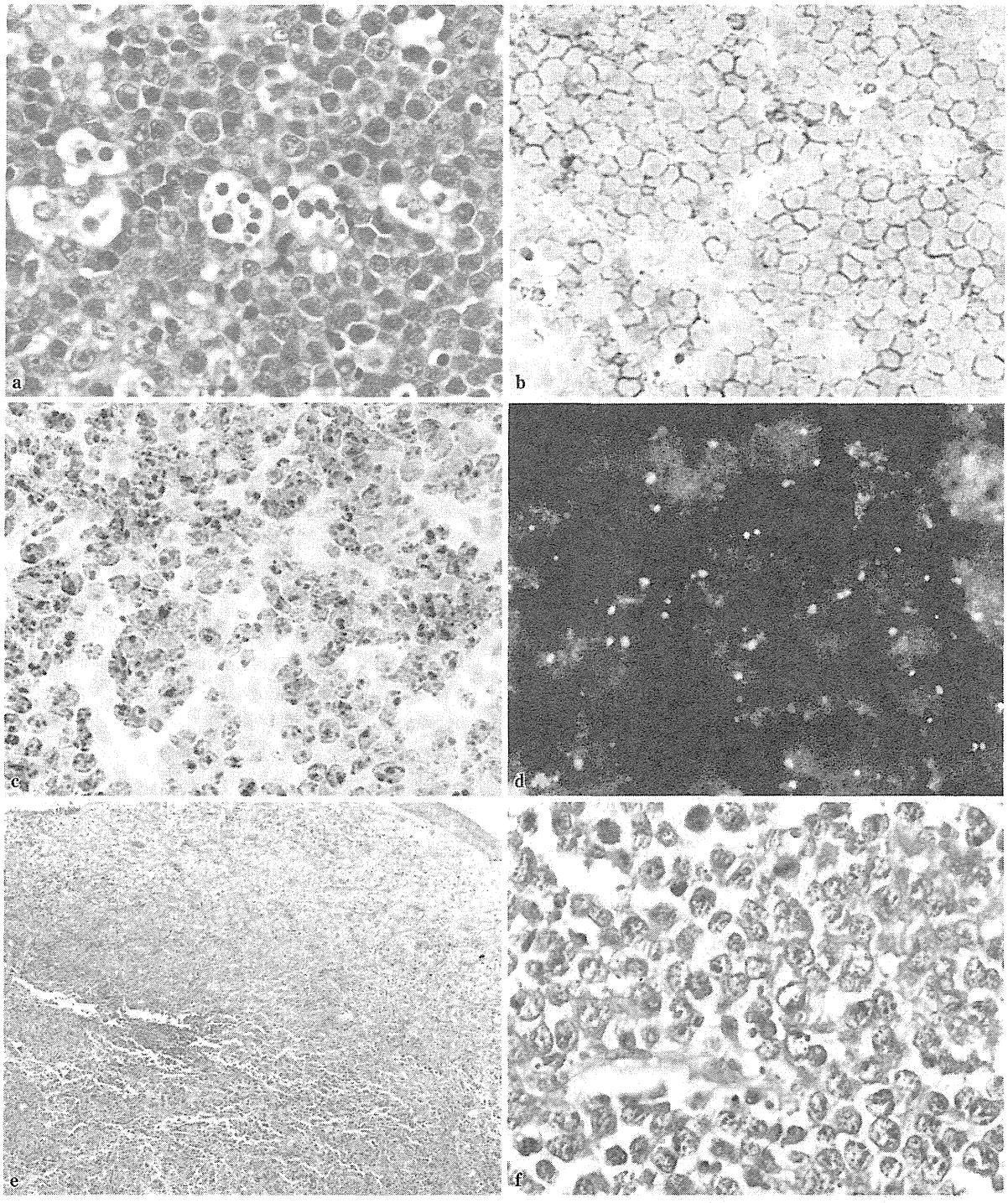

図1　BL　a～d：症例1．腫瘍細胞は大小不同で，やや多形性を示す(a)．CD10陽性(b)，MIB1＞90%(c)．FISH法では，*IGH/myc*遺伝子転座による融合シグナルが検出された(d；green＝*IGH*，orange＝c-*myc*)．e, f：症例2．やや大型の細胞がびまん性に増殖し，starry sky像はみられない．形態的にはBLは考えにくいが，CD20(＋)，CD79a(＋)，CD10(＋)，BCL2(－)，BCL6(＋)，MIB1＞90%，EBER(－)であり，免疫染色のパターンと*IGH/myc*(＋)であったことより，BLと考えられる．

WHO分類 第4版では健常人のリンパ腫として，intermediate BL/DLBCL（正式名称はB-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma）が提唱されている[6]．しかし，エイズ関連リンパ腫に対してこの亜型は定義されていない．WHO分類 第4版の記載では，この亜型はBLとDLBCLの中間的な腫瘍とも読めるが，近年では*myc*遺伝子と免疫グロブリン関連遺伝子の転座および*bcl2*，*bcl6*遺伝子と免疫グロブリン関連遺伝子の転座が2重もしくは3重に発生した腫瘍（double hit lymphoma, triple hit lymphoma）を主に扱う傾向にあり，単に診断がBLかDLBCLか悩むからという理由でこの亜型を用いることは推奨されない．エイズ関連リンパ腫でdouble hit lymphoma，triple hit lymphomaはほとんどみられないため，誤解を招かない意味でも，この診断名は避けたほうがよいと思われる．

2. diffuse large B-cell lymphoma (DLBCL)，NOS

大型Bリンパ球がびまん性に増生している腫瘍である[7]．本邦ではリンパ腫全体の1/3程度を占める最も一般的な組織亜型である．高齢者に多いが，あらゆる年齢に発症する．形態学的にはcentroblastを主体としたもの（centroblastic variant）が多いが，immunoblastが多いもの（immunoblastic variant）や細胞異型の強いanaplasticな形態をとることもある（anaplastic variant）．

エイズ関連リンパ腫における亜型としては，centroblastic variantが多いが，様々な割合でimmunoblastが混ざる．WHO分類 第4版ではcentroblastic variantはエイズ関連リンパ腫の25～30%を占め，その約3割がEBV陽性としている[4]．BLとの鑑別が問題になるのも主にこのcentroblastic variantである．一方で，immunoblastが90%以上を占めるimmunoblastic variantもエイズ関連リンパ腫の10%程度を占める．エイズ関連DLBCL, immunoblastic variantは90%がEBV陽性である．中枢神経原発のリンパ腫は通常，このimmunoblastic variantであり，脳の血管周囲にEBER（EBV encoded RNA）陽性のリンパ腫細胞の浸潤がみられる．HAART導入前の日本のエイズ関連リンパ腫ではDLBCL, immunoblastic variantが最も多かったが，最近は減少傾向にあり，無治療の，いわゆる「いきなりエイズ」例にみられる．

3. Hodgkin lymphoma (HL)

HLはリンパ節に系統的に進展する疾患であり，頸部に好発する．亜型としては結節性リンパ球優位型HL，古典的HLがあり，古典的HLにはさらにリンパ球豊富型lymphocyte rich（LR），結節硬化型nodular sclerosis（NS），混合細胞型mixed cellularity（MC），リンパ球減少型lymphocyte depleted（LD）がある．若年者と高齢者の二峰性の年齢分布が知られており，これはNS（若年者）とMC（高齢者）の2つの主な亜型のピークと一致する．組織像は，特徴的で非常に大型の腫瘍細胞（Hodgkin細胞）が散在性にみられ，周辺には小型の反応性リンパ球や好酸球が多数みられる．

エイズ関連HLは，奇妙なことに，HAARTの導入により発症率が上昇している[8]．特にHAARTによりCD4が150～200程度に回復してきた患者に発症率が高い．ほとんどの症例はMCかLDであり，NSも散見される．エイズ関連HLのほぼ全ての症例がEBV陽性であり，Hodgkin細胞はLMP1（latent membrane protein 1）とEBERを発現する．

免疫不全に関連した臓器移植後リンパ増殖性疾患やmethotrexate関連リンパ増殖性疾患では，HLに類似したリンパ増殖性疾患が知られている．これは典型的Reed-Sternberg細胞とするにはやや小型のEBER陽性細胞が散在性にみられ，それらはCD20＋，CD15－のことが多く，HL-like feature等の名前で呼ばれる．エイズ関連リンパ腫では少ない．

4. plasmablastic lymphoma

形質細胞とほぼ同じ免疫表現型をもち，形態的にはimmunoblastに似た細胞がびまん性に増殖するリンパ腫であり，主に口腔に発症する[9]（**図2**）．免疫染色ではCD138，CD38，Vs38c，IRF4/MUM1陽性，CD45，CD20，PAX5陰性で，CD30，EMAは高頻度に陽性である．EBVはほぼ全例が陽性であり，HHV-8は常に陰性である．ほとんどHIV陽性者にしか発症せず，他の患者では極めて稀である．口腔以外の症例もあり，今回検討した中でも肛門部のみに発症した症例があった．また，場所によっては形質細胞の形態とは乖離しているようにみえる症例もあり，免疫染色とEBERの*in situ* hybridization（ISH）は重要である．

5. primary effusion lymphoma (PEL)

胸水，腹水，心嚢水などに発症するHHV-8関連のCD20陰性の液性リンパ腫である[10]．通常固形腫瘍をつくらないが，胸膜や皮膚などへの浸潤巣をつくる（**図3**）．また，稀に皮膚，消化管，肺などに固形腫瘍として現れるものがあり，これらはextracavitary PELとして扱う．ほとんどHIV陽性男性同性愛者にのみ発症し，約半数はKaposi肉腫を合併している．形態学的には大型のimmunoblast様から，anaplastic

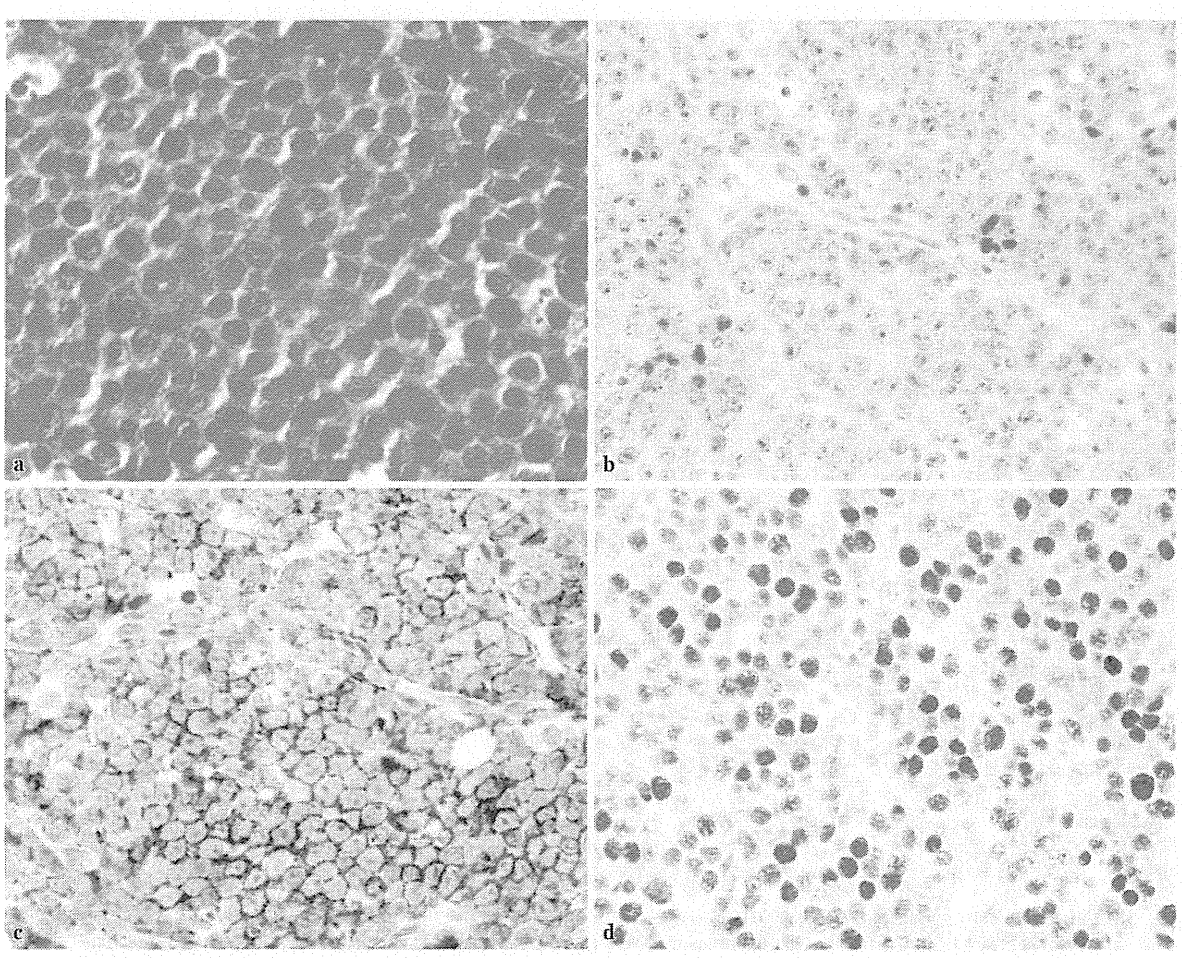

図2　plasmablastic lymphoma　歯肉生検材料．immunoblast様の細胞形態をとり(a)，CD20陰性(b)，CD138陽性(c)．EBER1-ISH法で陽性シグナルを認める(d)．

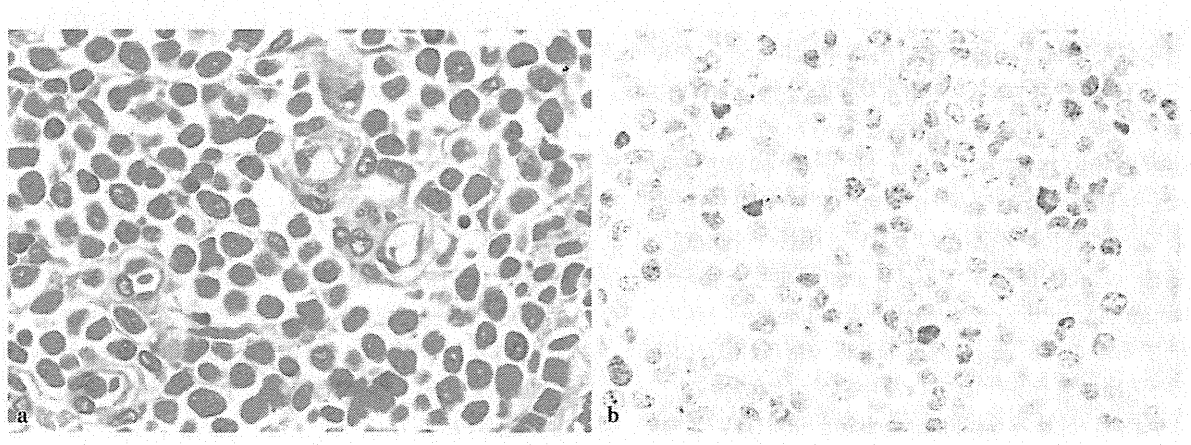

図3　PEL　extracavitary PELの症例．a：腸管に大型芽球様細胞のびまん性浸潤がみられた．核は偏在し，一部では車軸状にみえる．細胞質は形質細胞に似る．b：免疫染色ではこれらの細胞の核内にHHV-8 LANA1の陽性シグナルがみられる．

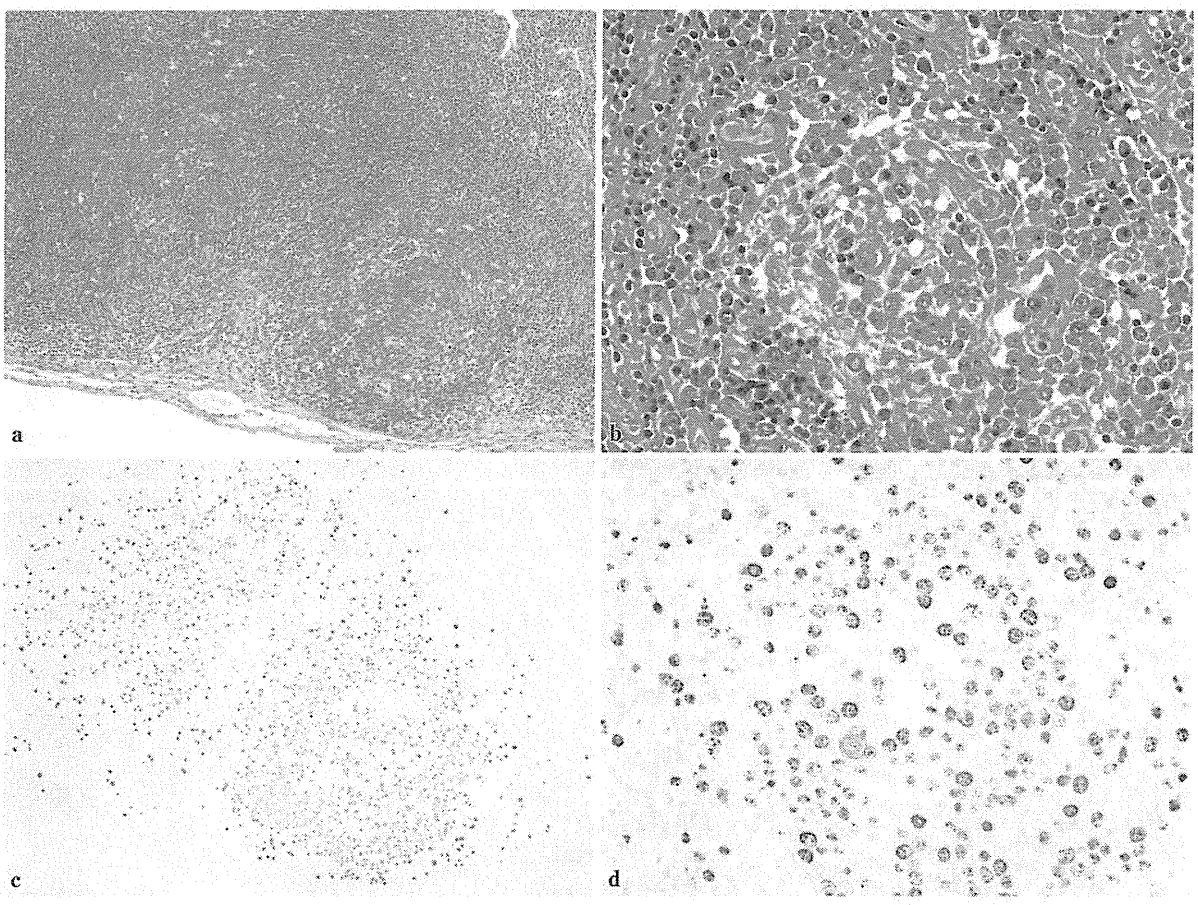

図4 large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease a, b：HE染色ではCastleman病に特徴的な硝子化した胚中心にplasmablasticな形態をもつリンパ腫細胞の浸潤が認められる．c, d：LANA1の免疫染色では，リンパ腫細胞がLANA1陽性であり，LANA1陽性細胞はリンパ濾胞暗殻から濾胞間組織に広がっている．

large cell様，plasmablasticな形態まで様々である．大型で不整な核は，明瞭で大きな核小体をもつ．免疫染色ではHHV-8 LANA1が常に陽性であり，HHV-8が陰性のものはPELの範疇には含めない．CD138, CD45, CD45RO (UCHL-1), CD30, EMA, EBERはしばしば陽性，CD20, CD79a, CD19, BCL-6は陰性である．他のリンパ腫とはHHV-8陽性である点で区別され，また，後述するHHV-8に関連した多巣性Castleman病(multicentric Castleman disease：MCD)に合併するリンパ腫とは，MCD併発の有無と，PELが通常cIgM, λを発現していない点で区別できる．

6. large B-cell lymphoma arising in HHV-8 associated multicentric Castleman disease (MCD) [=HHV-8 positive plasmablastic lymphoma, microlymphoma]

HHV-8に関連したMCDに合併するリンパ腫であり，HHV-8 LANA1, vIL-6, cIgM, λが陽性である[11] (図4)．CD20, CD79a, CD138, EBERは陰性の症例が多い．HIV陽性男性同性愛者にのみ発症し，Kaposi肉腫合併例が多い．HHV-8に関連したMCDに合併している必要があるが，HHV-8 LANA1, cIgM, λ陽性の細胞がシート状に増生している像がみられると間接的にこのリンパ腫を疑う．上記のPELとはPELがcIgM, λを発現していない点，PELは通常EBVが共感染している点で区別ができる．上記の口腔に発症するEBV陽性のplasmablastic lymphomaはHHV-8陰性であり，異なる疾患であることを留意されたい．

7. その他：エイズ関連リンパ腫として頻度の低いもの

WHO分類 第4版ではエイズ関連リンパ腫の稀な病型として，MALT lymphoma, peripheral T and NK-

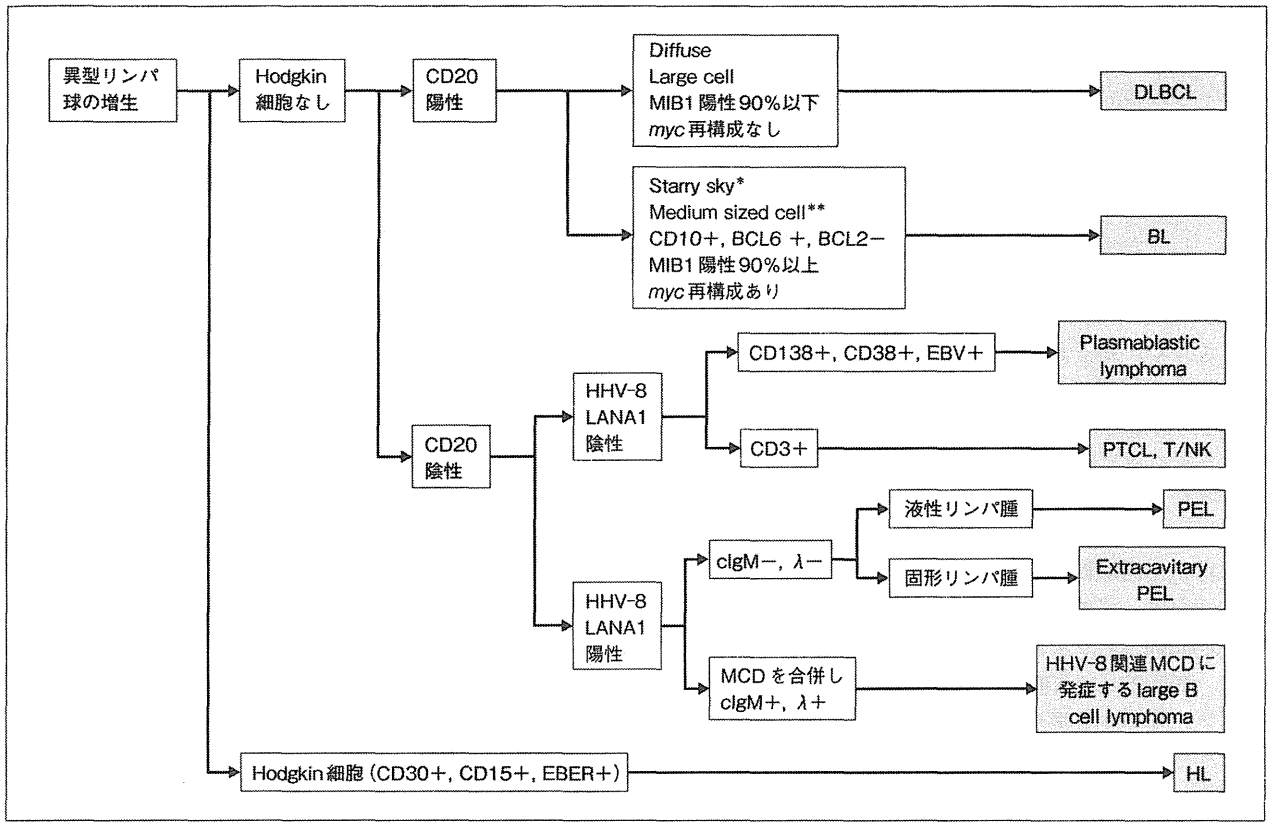

図5　エイズ関連リンパ腫診断のためのフローチャート　CD20陽性の場合，BL，DLBCLの鑑別が必要である．エイズ関連BLではstarry skyは必ずしも明瞭ではなく(*)，細胞の大きさも大型細胞が混ざることが多い(**)．形態的にBLとして典型的でなくても，CD10，BCL6，BCL2，MIB1の免疫染色と*myc*の再構成の結果がBLとして矛盾しなければ，BLに分類する．CD20陰性の症例ではHHV-8，EBVの検索を行い，HHV-8陽性であればPELかlarge B-cell lymphoma arising in HHV-8-associated MCDのどちらかに分類される．後者はHHV-8関連MCDに合併し，cIgM，λ陽性である点がPELとの鑑別点である．PELと同じ免疫学的表現型をもち，体腔以外に固形腫瘍を形成するHHV-8陽性リンパ腫はextracavitary PELに分類する．CD20陰性，CD138ないしCD38陽性，EBV陽性，HHV-8陰性でplasmablasticな形態をもつリンパ腫はplasmablastic lymphomaに分類する．HLはCD30陽性，CD15陽性，EBV陽性のHodgkin細胞が診断の決め手となる．

cell lymphoma，polymorphic lymphoid proliferations resembling PTLD (post-transplant lymphoproliferative disease) を挙げている．今回の検討では後2者の症例に加え，多発性骨髄腫の症例があった．また，日本では成人T細胞性白血病リンパ腫adult T-cell leukemia/lymphoma (ATL) と合併した例も知られている．

Ⅱ．エイズ関連リンパ腫の診断

診断過程のフローチャートを**図5**に示す．エイズ関連リンパ腫はどの組織型にしても非典型的な像をとるものが少なからず存在する．BL，DLBCLの鑑別は重要で，CD20，CD10，BCL6，BCL2，MIB1の免疫染色と*myc*の遺伝子再構成検査は必須である．エイズ関連リンパ腫ではBLの頻度が高いので，生材料を確保し，*myc*の遺伝子再構成を検査しておくことが重要である．典型的なDLBCLの形態像をとる症例はDLBCLとすべきであるが，BLを思わせる像があり，免疫染色，*myc*の遺伝子再構成の結果がBLと一致しているものであれば，BLと診断すべきである．また，日本のBLはエイズ関連のものでもEBV陰性のものが多い．BLとの鑑別が重要となるDLBCL, centroblastic variantにはEBV陽性のものと陰性のものがある．CD20陽性リンパ腫で以前から多い病型はEBV陽性DLBCL, immunoblastic variantであり，中枢神経原発のリンパ腫はほとんどこの病型である．エイズ患者にはCD20陰性のB細胞性リンパ腫もしばしば発

症する．こうした症例ではHHV-8，EBVの検索が重要である．エイズ患者に発症するHLは日本では頻度は低いものの，散見される．CD30陽性，CD15陽性，EBV陽性のHodgkin細胞が診断の決め手となる．

おわりに

日本におけるエイズ患者，およびHIV感染者数の増加に伴い，エイズ関連リンパ腫の症例数も確実に増加している．エイズに合併する悪性腫瘍としてはKaposi肉腫の頻度が高いが，Kaposi肉腫は特徴的な組織像と，最近ではLANA1の免疫染色のおかげで病理診断はそれほど難しくない．一方で，リンパ腫はここで挙げたような多彩な病態を含み，診断に苦慮する例が多い．今回，検討した症例は免疫染色に加え，*myc*の遺伝子再構成検査など，病理学的によく解析されたものであり，こうした症例を数多く供覧したことで，日本の症例におけるおおよその傾向をつかむことができた．検討会には治療にあたる臨床医にも参加していただき，担当した個々の症例について貴重なコメントをいただいた．特に問題となったBLとDLBCLの鑑別では，形態的な特徴と免疫染色，遺伝子検査の結果が乖離した症例が多くみられたが，こうした症例にはaggressiveな経過をとったものが多いというコメントが，上記の結論に至るまでの重要な情報となった．なお，BLとDLBCLの鑑別に関してはWHO分類 第4版の記述内容に不明な点があったため，WHO分類の筆者に直接コンタクトをとり，正確を期した．我々の検討内容の一部はWHO分類 第4版の筆者らにも回覧され，有意義なコメントをいただいた．本稿における結論はこれらのコメントを考慮したものであり，国際的にも通用するものと考えている．近年増えているHHV-8関連リンパ腫では，患者が男性同性愛者か，Kaposi肉腫合併の有無などが診断上，重要な情報となる．エイズ関連リンパ腫の診断に限らないが，臨床からの十分な情報が病理診断には必要不可欠である点を強調したい．また，今回の病理診断のコンセンサスを基に，今までの日本のエイズ関連リンパ腫症例を再検討し，統計の見直しを行う必要が感じられた．今後増え続けるであろうエイズ関連リンパ腫の診断の手引きとしてこの総説を利用していただければ幸いである．

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