Variations in clinical presentation, frequency of hemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographical regions

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ABSTRACT

Background and Objectives

This study explored variations in the clinical manifestations of intravascular lymphoma (IVL) on the bases of the association with hemophagocytosis and the country where the diagnosis was made.

Design and Methods

The clinical features of 50 Western patients with IVL were compared with those of 123 patients with IVL diagnosed in Eastern countries (87 diagnosed in Japan and 36 in other Asian countries), previously reported in English literature, and collected by an electronic bibliographic search.

Results

Hemophagocytosis was absent in Western patients, but reported in 38 (44%) Japanese patients (p=0.00001) and in seven (19%) patients from other Asian countries (p=0.002). No clinical differences were evident between patients with hemophagocytosis-negative IVL diagnosed in Western countries, Japan and other Asian Countries. Conversely, Japanese and non-Japanese patients with hemophagocytosis-related IVL more frequently had stage IV disease, fever, hepato-splenic involvement, marrow infiltration, dyspnea, anemia, and thrombocytopenia, and rarely exhibited cutaneous or central nervous system involvement. Lymph node and peripheral blood involvement was uncommon in all subgroups. In Western patients, anthracycline-based chemotherapy was associated with a 52% remission rate, and a 2-year overall survival of 46%.

Interpretation and Conclusions

The clinical features of IVL vary according to the association with hemophagocytosis, regardless of the country in which the diagnosis is made. Western, Japanese and other Asian patients with hemophagocytosis-negative IVL display similar clinical characteristics and should be considered as having *classical* IVL. Patients with hemophagocytosis-related IVL show significantly different clinical features. Both forms have a poor prognosis. Extensive molecular studies are needed to explore whether these clinical differences might reflect discordant biological entities within IVL.

Key words: intravascular lymphoma, hemophagocytosis, cutaneous lymphoma, brain lymphoma.

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Intravascular lymphoma (IVL) is a rare entity characterized by exclusive or predominant growth of neoplastic cells within the lumen of blood vessels. This disorder was recently recognized as a subtype of diffuse large B-cell lymphoma by the World Health Organization (WHO) Classification,[1] although rare forms with a T-cell phenotype also occur.[2] The understanding of IVL is very limited considering that, with a few exceptions,[3,4] literature on this malignancy is almost exclusively represented by case reports and small case series.[5-7] IVL is considered to be a rapidly aggressive and disseminated disease, usually affecting elderly patients, and is associated with a poor performance status (PS), B symptoms, anemia, and elevated serum lactate dehydrogenase (LDH) levels.[4] However, the clinical presentation, behavior and therapeutic outcome are extremely variable; in particular, it has been suggested that there are some differences in clinical and histopathological characteristics between patients diagnosed in Asian and Western countries.[3,4,8,9] A large Japanese study concluded that IVL associated with hemophagocytosis (HPC) is the equivalent of the *Asian variant of IVL*.[4] In Western patients, a *cutaneous variant*, with a favorable clinical behavior, has been described.[4] However, a comprehensive and detailed comparison between relatively large series from Western and Eastern countries has not previously been performed, and clinical and biological differences among these cohorts of patients are still debated. The acknowledgement of the existence of different clinical forms may have diagnostic, prognostic and therapeutic implications and constitutes the rationale for further investigations into the mechanisms of lymphomagenesis, adhesion and dissemination.[10] This paper reports a comparison of presenting symptoms, clinical features, behavior, and therapeutic management of the largest series of patients with IVL diagnosed in Western countries with three potentially different subgroups of previously reported cases of IVL diagnosed in Asian countries, in order to assess whether apparent clinical differences may be driven by the geographical distribution of IVL patients.

Design and Methods

Study group (Western-IVL series)

A questionnaire requesting information about patients' characteristics, clinical presentation, diagnosis, staging, sites of disease, laboratory findings, treatment, objective response, site and date of relapse, second line treatment, survival, salient morphologic features, and autopsy findings was sent to each participating center of the International Extranodal Lymphoma Study Group (I.E.L.S.G.). Criteria for including patients were a histological diagnosis of IVL and no evidence of human immunodeficiency (HIV-1) infection or other immunodeficiency. Thirty centers from ten countries provided retrospectively collected, clinical and pathological data on 50 HIV-negative patients with an *in vivo* (n=38) or *post-mortem* (n=12) histological diagnosis of IVL (from 1985 to 2006), which constituted the Western-IVL series. Preliminary data of a part of this series have been reported previously.[4]

Eastern cases

Features of the Western-IVL series were compared with those of cases of IVL diagnosed in Eastern countries and previously reported in English literature. An electronic search of Medline, Current Contents and Pubmed, updated to March 2006, was performed, including as key words *intravascular lymphoma*, *intravascular lymphomatosis*, *angiotropic lymphoma*, *angioendotheliomatosis*, and *hemophagocytosis*. Each full paper was reviewed and duplicate reports describing the same patients were included just once. We found 123 previously reported cases of IVL diagnosed in Japan (n=87) and other Asian countries (n=36) [see references in the linked file]. These groups were divided accordingly to the country in which the diagnosis was made and to the presence of HPC, which was defined by the morphologic recognition of an excess of mature *benign-looking* histiocytes with phagocytosis of erythroblasts, granulocytes and platelets in histopathological specimens. Therefore, three main comparator groups were considered: 1) Japanese patients with IVL and HPC (J-HPC), 2) Japanese patients with IVL but without HPC (J-IVL), and 3) patients with IVL without HPC diagnosed in Asian countries other than Japan (Eastern-IVL). Additionally, a small subgroup of patients with IVL and HPC diagnosed in Western and Asian countries other than Japan and previously reported in English literature was considered for analysis [see references in the linked file].

Statistical considerations

The distributions of clinical variables among the subgroups of patients were assessed by Fisher's exact test for categorical variables. Survival curves were generated by the Kaplan-Meier method. Overall survival (OS) was calculated from the date of pathologic diagnosis to death or to the last date of follow-up, while event-free survival (EFS) was calculated from the first day of treatment to relapse, progression or death, or to the last date of follow-up. The impact of clinical and therapeutic variables on survival was evaluated using the log-rank test. All the probability values were two-sided, with an overall significance level of 0.05. Analyses were carried out using the Statistica 4.0 statistical package for Windows (Statsoft Inc, 1993, Tulsa, OK 74104, USA).

Results

Study Population

HPC was absent in the 50 Western-IVL cases, but was reported in 38 (44%) of the 87 Japanese patients (p=0.00001) and in seven of the 36 patients (19%) diagnosed in other Asian countries (p=0.002). Accordingly, the three main groups against which to compare the Western-

Table 1. Clinical features in our series (Western), in Japanese cases with (J-HPC) or without (J-IVL) hemophagocytosis and in patients with IVL without hemophagocytosis from Eastern countries other than Japan (Eastern-IVL).

		J-HPC		*J-IVL*		*Eastern-IVL*	
Variable	*Western series*	*series*	*p#*	*series*	*p#*	*series*	*p#*
Number of patients	50	38	49			29	
Median age (range)	68 (34-90)	67 (44-78)	NS	69 (13-82)	NS	62 (34-81)	NS
Male gender	23 (46%)	19 (50%)	NS	24 (49%)	NS	14 (48%)	NS
Previous or concomitant cancer	9 (18%)	4 (11%)	NS	2 (4%)	0.02	2 (7%)	NS
Stage IV	38 (76%)	37 (97%)	0.004	40 (82%)	NS	23 (79%)	NS
Fever	21 (42%)	33 (87%)	0.00001	23 (47%)	NS	18 (62%)	NS
Fatigue	11 (22%)	17 (45%)	0.03	8 (16%)	NS	5 (17%)	NS
Jaundice	0 (0%)	10 (26%)	0.0002	0 (0%)	NS	2 (7%)	NS
Cutaneous lesions	19 (38%)	1 (3%)	0.0001	12 (24%)	NS	3/18 (17%)*	NS
Neurological involvement	21 (42%)	8 (21%)	0.03	26 (53%)	NS	10 (34%)	NS
Hepatic involvement	13 (26%)	25 (66%)	0.0002	15 (31%)	NS	14 (48%)	0.05
Splenic involvement	13 (26%)	29 (77%)	0.00001	10 (20%)	NS	12 (41%)	NS
Bone marrow involvement	15 (30%)	28 (74%)	0.0001	17 (35%)	NS	11 (38%)	NS
Lymphadenopathy	4 (8%)	2 (5%)	NS	2 (4%)	NS	5 (17%)	NS
Peripheral blood involvement	2 (4%)	5 (13%)	NS	0/26 (0%)*	NS	0 (0%)	NS
Pulmonary involvement	9 (18%)	14 (37%)	0.04	13 (27%)	NS	7 (25%)	NS

*NS: not significant; NR: not reported; *Relationship between number of positive cases and number of assessed cases; #p values for comparisons between the Western series and the other subgroups.*

IVL series consisted of 38 J-HPC patients, 49 J-IVL patients and 29 Eastern-IVL patients. Additionally, a small subgroup of patients with IVL and HPC diagnosed in Western (n=5) and Asian countries other than Japan (n=7) and previously reported in English literature was considered for analysis.

Clinical presentation

Comparisons of the patients' characteristics at diagnosis between the Western-IVL series and the three main groups of Asian patients are summarized in Table 1. The number of patients with an *in vivo* diagnosis was 38 (76%) Western-IVL, 35 (92%) J-HPC, 36 (74%) J-IVL, and 16 (55%) Eastern-IVL. No significant differences in age and gender were observed among the subgroups.

The clinical presentation was heterogeneous in Western-IVL patients, with a remarkable deterioration in PS, with an ECOG score ≥2 in 32 cases (64%). PS was rarely reported in Asian series, but the constant presence of systemic symptoms and multi-organ involvement in reported cases suggests that IVL is associated with a poor PS also among Asian patients. As reported in Table 1, with a few exceptions, no significant differences in clinical features were observed among Western-IVL, J-IVL and Eastern-IVL subgroups. Conversely, several significant differences were observed between these three subgroups and patients with J-HPC. Thirty Western-IVL patients (60%) had systemic symptoms, mostly represented by fever, which was present in 21 cases (42%), and associated with other B symptoms in 12 cases. Fever as well as fatigue and jaundice were significantly more common among J-HPC patients (Table 1). Significant differences in terms of Ann Arbor stage of disease and sites of disease were observed. A large majority of J-HPC patients had stage IV disease, which was observed in 76-82% of cases in the other subgroups (Table 1). The most common sites of disease in the Western-IVL series, i.e., skin (38%) and central nervous system (42%), were involved in a significantly lower proportion of cases in J-HPC patients (3% and 21%, respectively). In the J-IVL and Eastern-IVL subgroups, the percentages of involvement of skin and central nervous system were similar to those observed in the Western series (Table 1). Cutaneous lesions were the sole pathologic finding in 12 (24%) Western cases; these patients were considered as having a *cutaneous variant* of IVL. The *cutaneous variant* was diagnosed in 0%, 6% and 0% of J-HPC (p=0.0004), J-IVL (p=0.01) and Eastern-IVL (p=0.002) subgroups, respectively. Involvement of hemolymphatic organs was significantly more common in J-HPC cases: 66%, 77% and 74% of these patients showed liver, spleen and marrow involvement, respectively, which was present in 26%, 26% and 30% of Western-IVL patients (p=0.0002, 0.00001 and 0.0001, respectively). With the exception of slightly more common involvement of liver in Eastern-IVL patients, no significant differences in the involvement of hemolymphatic organs were observed among Western-IVL, J-IVL and Eastern-IVL subgroups (Table 1). There were no signifi-

Table 2. Laboratory findings in our series (Western), in Japanese cases with (J-HPC) or without (J-IVL) hemophagocytic features and in IVL cases from Eastern countries other than Japan (Eastern-IVL).

		J-HPC		*J-IVL*		*Eastern-IVL*	
Variable	*Western series*	*series*	*p#*	*series*	*p#*	*series*	*p#*
Number of patients	50	38		49		29	
Anemia	33 (66%)	32 (84%)	0.05	16/25 (64%)*	NS	19 (66%)	NS
Leukopenia	11 (22%)	11 (29%)	NS	4/25 (16%)*	NS	6 (21%)	NS
Thrombocytopenia	16 (32%)	28 (74%)	0.0003	7/25 (28%)*	NS	14 (48%)	NS
High serum LDH levels	33/39 (85%)*	36/36 (100%)*	0.02	31/33 (94%)*	NS	21/23 (91%)*	NS
High β2-microglobulin	16/19 (84%)*	NR		NR		NR	
Elevated ESR	22/46 (48%)*	NR		NR		NR	
Monoclonal component	7/45 (16%)*	5 (13%)	NS	1/20 (5%)*	NS	NR	
High ALT levels	3 (6%)	10 (26%)	0.02	3 (6%)	NS	1/13 (8%)*	NS
High bilirubin levels	1 (2%)	11 (29%)	0.0008	0 (0%)	NS	2 (7%)	NS

*NS: not significant; NR: not reported; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; ALT: alanine amino transferase; *Relationship between number of positive cases and number of assessed cases; #p values for comparisons between the Western series and the other subgroups.*

cant differences in lymph-node and peripheral blood involvement among the four studied subgroups, infiltration rates ranged between 4% and 17% and between 0% and 13%, respectively (Table 1).

Histopathological and laboratory findings

In the 38 Western-IVL patients with an *in vivo* diagnosis, the histopathological diagnosis was performed on tissue samples obtained by partial surgical biopsy in 29 cases (skin in 18 cases, central nervous system in five, lung in two, uterus in two, gallbladder in one, and liver in one), visceral resection in six (kidney in three, prostate in two and spleen in one) and bone marrow biopsy in three cases. By definition, all cases from the four subgroups showed large lymphoid cells within vessel lumina (Figure 1). Lymphomatous lesions with infiltration of extravascular tissues (called *extravascular component*) were observed in ten (20%) Western cases, and was significantly more common in samples from lung and kidney of J-HPC cases. All Western-IVL cases but one displayed a B-cell immunophenotype. T-cell immunophenotype was observed in one (2%) Western-IVL case, in one (3%) J-HPC case, in one J-IVL (2%), and in five (17%) Eastern-IVL cases ($p \leq 0.03$ between Eastern-IVL cases and the other three groups; not significant differences among the others).

As reported in Table 2, no significant differences in laboratory findings were noted among Western-IVL, J-IVL and Eastern-IVL subgroups; while a different biochemical profile was observed in J-HPC patients. In fact, anemia (84%) and thrombocytopenia (74%) were significantly more common in J-HPC cases than in the other three subgroups. Thrombocytopenia was associated with anemia, bone marrow infiltration and hepato-splenic involvement in each subgroup. Increased serum LDH levels were observed in all J-HPC patients and in 85%-94% of cases in the other subgroups (Table 2). Increased levels of β_2-microglobulin and elevated erythrocyte sedimentation rates were observed in, respectively, 84% and 48% of Western-IVL cases, while these parameters were not reported for patients in the other subgroups. A monoclonal serum component was reported in 5% - 16% of cases in the studied subgroups (p= not significant). Elevated transaminases and total bilirubin levels were significantly more common among J-HPC cases than in the other subgroups (Table 2).

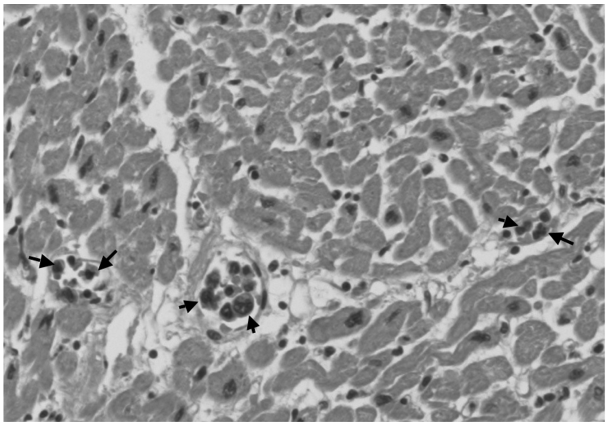

Figure 1. Intravascular lymphoma of the cardiac muscle (hematoxylin and eosin). The growth of neoplastic large cells (arrows) occurs within the lumen of blood vessels. Neoplastic lymphocytes show large nuclei with one or more nucleoli and scant cytoplasm.

Comparison with patients with HPC-related IVL diagnosed outside Japan

The Western-IVL series was also compared with the small group (n=12) of patients with HPC-related IVL diagnosed in Western (n=5) or Eastern (n=7) countries other than Japan and previously reported in English literature

[*see references in the linked file*] to better understand whether clinical features are related to HPC independently of the country of origin of the patient. As reported in Table 3, these patients exhibited similar characteristics to J-HPC patients, while displaying many differences compared to Western-IVL patients. Similarly to J-HPC patients, patients with HPC-positive IVL diagnosed outside Japan more commonly had stage IV disease, fever, thrombocytopenia, and involvement of liver, spleen and bone marrow. A higher prevalence of cutaneous lesions in non-Japanese patients with HPC-positive IVL was the only distinctive feature in comparison with J-HPC patients (Table 3).

Therapeutic outcome

In Western-IVL series, *in vivo* diagnosis was possible in 38 patients, 36 of whom received at least one line of treatment. Seventeen (47%) achieved a complete remission (CR) and four had a partial response (PR), for an overall response rate of 58%; nine patients experienced progressive disease (PD), two had stable disease, and four died of toxicity. There were 23 treatment failures: 11 PD, eight relapses after response and four toxic deaths, All treatment failures but one occurred within the first year of follow-up. Anthracycline-based chemotherapy was administered as initial treatment to 25 patients, resulting in a CR rate of 52%, a median OS of 10+ months and a 2-year OS of 46±10%. The median EFS for the 38 patients with an *in vivo* diagnosis was 6 months (range 1-81), with a 2-year EFS of 32±8%. Seventeen patients are alive at a median follow-up of 28 months, with a 2-year OS of 39±8%. Considering the entire series (including patients with a *post-mortem* diagnosis), the 2-year EFS and OS were 24±6% and 30±7%, respectively.

Discussion

The comparison of our series, the largest one of IVL patients diagnosed in Western countries, with IVL cases from Asian countries strongly suggests the existence of different clinical forms of IVL. This issue does not seem simply to reflect regional differences since IVL cases with similar clinico-pathological characteristics have been reported in Western countries, in Japan and in other Asiatic countries (the Western-IVL, J-IVL and Eastern-IVL groups in this study). Patients from these three subgroups could be comprehensively considered as having the *classical form* of IVL. By contrast, patients with IVL associated with HPC, who have been mostly reported in Japan (the J-HPC group in this study), display clinical features distinct from those observed in the patients with the *classical form*. Patients with IVL and HPC diagnosed in countries other than Japan display similar characteristics to those of J-HPC patients, while Japanese patients with IVL without HPC (the J-IVL group) show similar features to those of Western patients. Taken together, these data suggest that differences in clinical presentation and behavior in IVL

Table 3. Clinical features and laboratory findings in patients with IVL and hemophagocytic features (HPC) diagnosed in Western or Eastern countries other than Japan in comparison with our series (Western) and J-HPC patients

	Non-Japanese pts with IVL and HPC	*Western series*		*J-HPC*	
Variable		*series*	*p#*	*series*	*p#*
Number of patients	12	50		38	
Median age (range)	60 (54-77)	68 (34-90)	NS	67 (44-78)	NS
Male gender	6 (50%)	23 (46%)	NS	19 (50%)	NS
Stage IV	12 (100%)	38 (76%)	0.04	37 (97%)	NS
Fever	11 (92%)	21 (42%)	0.002	33 (87%)	NS
Jaundice	2 (17%)	0 (0%)	0.008	10 (26%)	NS
Cutaneous lesions	4 (33%)	19 (38%)	NS	1 (3%)	0.009
CNS involvement	2 (17%)	21 (42%)	0.02	8 (21%)	NS
Hepatic involvement	7 (58%)	13 (26%)	0.03	25 (66%)	NS
Splenic involvement	7 (58%)	13 (26%)	0.03	29 (77%)	NS
Marrow involvement	9 (75%)	15 (30%)	0.007	28 (74%)	NS
Lymphadenopathy	1 (8%)	4 (8%)	NS	2 (5%)	NS
Lung involvement	3 (35%)	9 (18%)	NS	14 (37%)	NS
Anemia	9 (75%)	33 (66%)	NS	32 (84%)	NS
Leukopenia	4 (33%)	11 (22%)	NS	11 (29%)	NS
Thrombocytopenia	10 (83%)	16 (32%)	0.003	28 (74%)	NS
High serum LDH levels	11 (92%)	33/39 (85%)*	NS	36/36 (100%)*	NS
High ALT levels	5 (42%)	3 (6%)	0.006	10 (26%)	NS
High bilirubin levels	5 (42%)	1 (2%)	0.0008	11 (29%)	NS

*NS: not significant; NR: not reported; CNS: central nervous system; PB: peripheral blood; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; ALT: alanine amino transferase; *Relationship between number of positive cases and number of assessed cases. #p values for comparisons between the group of patients with IVL and HPC diagnosed in countries other than Japan and the other subgroups.*

might be more related to the concomitant presence of HPC rather than the geographical distribution of the disease *per se*.

This study is the first one comparing large series of IVL patients diagnosed in different geographical regions. The study of cumulative retrospective series and comparison with previously reported cases is so far the only strategy available for studying IVL given the extreme rarity of this disease and the diagnostic difficulties. Conclusions from this study should be viewed with caution, not only because of the intrinsic caveats regarding the methods used, but also considering that cases published in non-English literature were not included in this analysis, which may have introduced some interpretation biases. Nevertheless, the size of the studied subgroups, the high proportion of patients with an *in vivo* diagnosis and the quality of reports in English literature support our conclusions. Moreover, the clinical features observed in the J-HPC and J-IVL subgroups have been confirmed by a recently reported study including the largest series of Japanese patients with IVL (n=96).[11] Our observations suggest that, unlike in Japanese patients,[8] HPC is rarely observed in IVL cases diagnosed in Western countries. Among 321 cases of IVL diagnosed in Western countries, and published in English literature, morphologically confirmed HPC has been reported in only five cases (1.5%).[12-15] However, two of these patients showed HPC features only at relapse and not at initial diagnosis,[14,15] and two others were of Caribbean and Vietnamese origin.[12,16] Comprehensively, the rare cases of HPC-associated IVL diagnosed outside Japan exhibited clinical features similar to those displayed by patients with HPC-associated IVL diagnosed in Japan (J-HPC), i.e., significantly higher rates of advanced disease, fever, hepato-splenic involvement, bone marrow infiltration, fatigue, jaundice, dyspnea, anemia, thrombocytopenia, and altered liver function tests. In contrast, the skin and central nervous system, the most common sites of disease in the classical form of IVL, were rarely involved in J-HPC patients. To the best of our knowledge, there is a single case of cutaneous involvement in J-HPC patients, which was represented by a cutaneous lesion on the torso reported as a cutaneous induration without histological confirmation.[17] Our analysis demonstrates that other characteristics, such as age, gender and rates of lymph-node involvement, peripheral blood dissemination and increased serum LDH levels, overlap substantially between classical and HPC-related forms. Both forms share B-cell immunophenotype in >97% of cases, in contrast to other non-Hodgkin's lymphomas associated with HPC, which are mostly of T-cell lineage.[18] As reported for other hematologic malignancies,[19] the presence of HPC has been proposed as a negative prognostic factor in IVL patients. Unfortunately, the comparison of therapeutic outcomes among the studied subgroups was limited by the fact that data from Asian patients were collected from case reports written by physicians with different expertise and specializations, sometimes with incomplete therapeutic data (complete therapeutic data for 94% of previously reported J-HPC patients, 70% of J-IVL patients and 88% of Eastern-IVL patients) and minimal follow-up. In the largest cumulative series of Japanese patients with IVL,[11] the use of anthracycline-based chemotherapy, the standard strategy against IVL,[11,20] resulted in a 55% complete remission rate and a median OS of 13 months, which are very similar outcomes to those of the current series of Western-IVL patients. In the largest reported series of patients with the so-called Asian variant of IVL, anthracycline-based chemotherapy was associated with a complete remission rate of 53%, and a median OS of 10 months.[3] At the time of analysis, the combination of rituximab and chemotherapy has been reported to have been used in 15 patients (six in our series), resulting in complete remission in 11 of 12 evaluable patients, and no relapses at a median follow-up of 15 months; this combined strategy seems to be advisable in patients with CD20-positive IVL. Consolidation with high-dose chemotherapy supported by autologous stem cell transplantation may improve current outcomes,[21-23] even among J-HPC patients.[9] The application of such a strategy is, however, greatly limited by the high median age and poor PS of IVL patients. Thus, the identification of reliable high-risk predictors constitutes a relevant issue in the management of patients with IVL.

The virtually selective geographical distribution of the *HPC-related form* of IVL as well as its differences from the *classical form* could have environmental causes. In fact, IVL occurs in rural areas of Southwestern Japan, where human T-cell lymphotropic virus type-1 (HTLV-1) is endemic,[8] and associations with some helminthic infections have been proposed in J-HPC patients.[24] Associations between IVL and HTLV-1, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella-zoster virus and human herpes virus-6 have not been detected.[25] In conclusion, differences in clinical features of IVL seem to be correlated to the concomitant presence of HPC rather than to the geographical area where the lymphoma is diagnosed. At least two different clinical forms of IVL seem to exist: a *classical form*, which is the most common presentation in Western countries, with frequent involvement of the skin and central nervous system and less common infiltration of hemolymphoid organs; and a *HPC-related form*, which is remarkably more common in Japan, with an almost constant involvement of hemolymphoid organs, higher rates of advanced disease, fever, respiratory symptoms, anemia, and thrombocytopenia, and virtually always sparing the skin. Despite these clinico-pathological differences, patients with both forms have a poor prognosis when treated with anthracycline-based chemotherapy, and treatment intensification and the addition of rituximab appear advisable. Extensive phenotypic and molecular characterization is needed to test whether these different clinical forms may also have a different biological backgrounds, and, therefore, international co-operative studies are warranted.

Appendix

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Authors' Contributions

Substantial contributions to acquisition of data were made by O Bairey, M Martelli, A De Renzo, C Doglioni, C Montalbán, A Tedeschi, A Pavlovsky, S Morgan, L Uziel, M Ferracci, S Ascani, U Gianelli, C Patriarca, F Facchetti, A Dalla Libera, B Pertoldi, B Horvath, A Szomor. Acquisition of data, analysis and interpretation of data, drafting and revising the article were performed by AJM Ferreri, GP Dognini, E Campo, R Willemze, JF Seymour, E Zucca, F Cavalli, and M Ponzoni. All authors revised the manuscript and approved its final version.

Conflict of Interest

The authors reported no potential conflicts of interest.

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