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Retrospective study of intravascular large B-cell lymphoma cases diagnosed in Quebec

A retrospective study of 29 case reports

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Abstract

Introduction: Intravascular large B-cell lymphoma (IVL) is an extremely rare malignancy, mainly studied through European and Asian series. Due to the low incidence of this condition, our understanding of the clinical presentation as well as the management of IVL relies on a limited number of patients.

We report the largest North American study to date on IVL with 29 cases from Quebec hospital diagnosed between 1990 and 2016. The aim of our study is to describe the clinical presentations, diagnostic and staging procedures, therapeutic management and clinical outcomes of IVL patients in our population and compare the disease phenotype to European and Asian series reported.

In our cohort, all patients had stage IV IVL at diagnosis, with a median age of 66.7 years (range 47.2–90.8). Clinical presentation was characterized by constitutional symptoms (100%), poor ECOG-PS (100% ≥ 2), cytopenias (93% anemia), and elevated lactate dehydrogenase (97%) and C-reactive protein (96%). Our cohort presented with mainly cutaneous and neurological symptoms. However, neurological involvement (75.9%) was predominant and no "cutaneous variant" was observed; this differs from European literature, where "classical" IVL is reported with mainly cutaneous involvement. Two of our Caucasian patients presented "Asian variant" IVL; this observation is not unusual, as cases of "classical" IVL have been reported in Asians and "Asian variant" IVL has been reported in Europeans. All patients were classified according to their immunophenotypic features in 3 different subgroups ($CD5^+$ or $CD5^-CD10^+$, $CD5^-CD10^-$, $CD5^+CD10^-$) with no difference in outcome. Finally, 62% of our cohort received anthracycline-based chemotherapy and 53% of them achieved a complete response. After a median follow-up of 328 days, OS at 3 years was 42.7% for the entire cohort and 47.4% for the cases with in vivo diagnosis.

Conclusion: Unlike European studies on "classical" IVL, our study showed that the French Canadian presentation of this subtype of IVL is more frequently observed with neurological rather than cutaneous involvement. Finally, an early diagnosis is of primary importance since almost a quarter of patients receive a post-mortem diagnosis. A prompt diagnosis allows the introduction of an early treatment, associated with a CR in 53% of patients.

Abbreviations: 18FDG-PET/CT = 18FDG-positron emission tomography/computerized tomography, ANA = anti-nuclear antibody, anti-DNA = anti-DNA antibody, ARDS = acute respiratory distress syndrome, BM = bone marrow, CHOP = [cyclophosphamide, hydroxyadriamycine, oncovin, prednisone], CI = confidence interval, CNS = central nervous system, CR = complete response, CRP = C-reactive protein, CSF = cerebrospinal fluid, CT = computed tomography, DIC = disseminated intravascular coagulation, DLBCL = diffuse large B-cell lymphoma, EBV = Epstein–Barr virus, ECOG = eastern cooperative oncology group, EFS = event-free survival, ESHAP = [etoposide, methylprednisone, cytarabine, cisplatin], ESR = erythrocyte sedimentation rate, HDMTCX = high-dose methotrexate, HSCT = hematopoietic stem-cell transplantation, IPI = international prognostic index, ITMTX = intrathecal methotrexate, IVL = intravascular large B-cell lymphoma, LDH = lactate dehydrogenase, LP = lumbar puncture, MODS = multiple organ dysfunction syndrome, MRI = magnetic resonance imaging, NHL = non-Hodgkin lymphoma, OS = overall survival, PAH = pulmonary arterial hypertension, PR = partial response, PS = performance status, R-CHOP = [rituxan,

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cyclphosphamide, hydroxyadriamycine, oncovin, prednisone], RF = rheumatoid factor, R-GEMOX = [rituxan, gemcitabine, oxaliplatin], R-ICE = [rituxan, ifosfamide, etoposide, carboplatin], TIA = transitory ischemic attack, TTE = transthoracic echocardiogram.

Keywords: Canada, case series, intravascular lymphoma, multicenter, North America

1. Introduction

Intravascular large B-cell lymphoma (IVL) is characterized by the exclusive or predominant presence of lymphoma cells in the lumina of small vessels. Even though T-cell phenotype has been reported, IVL has been recently classified by the World Health Organization (WHO) Classification as a subtype of B-cell lymphoma.[1–5]

IVL is considered an aggressive, disseminated, and usually fatal malignancy that affects older individuals. Its initial clinical presentation varies according to geography. "Classical" IVL, mainly reported in Europe, is characterized by cutaneous and/or neurological involvement. "Asian variant" IVL, mainly reported in Asia, is characterized by hemophagocytic syndrome, bone marrow (BM) involvement, fever, hepatosplenomegaly, and/or thrombocytopenia.[6–8] These various clinical presentations contribute to delay in diagnosis and treatment.

Intravascular large B-cell lymphoma has been mainly studied through European and Asian series. Due to the low incidence of this condition, our understanding of the clinical presentation as well as the management of IVL rely on a limited number of patients.[9–21] Given the absence of a large North American series of IVL, we decided to perform a retrospective review of patients treated in Quebec, Canada. The aim of our study was to depict the different clinical presentations, the diagnosis and staging procedures performed, the therapeutic management and the clinical outcomes of IVL patients treated in Quebec, Canada. Data collected were then compared to reported series from Europe and Asia.

We retrieved 29 cases of IVL which corresponds, to the best of our knowledge, to the largest series reported in North America.

2. Patients and methods

2.1. Our case series

We performed a retrospective study in collaboration with Hematology-Oncology centers in Quebec. We included adults who were diagnosed with IVL in the province of Québec between 1990 and 2016. Data were collected by a single author (VB). Files of patients with the specific diagnostic code for IVL were obtained from each participating medical center archives and reviewed. Files of patients with diagnostic codes of "unspecified lymphoma" or "lymphoma (without any specification)" were reviewed as well to find IVL cases. The research was conducted after approvals from scientific and ethics committees (Comité d'éthique de la recherche en santé chez l'humain).

The following information was collected: demographic information, bioclinical features at diagnosis, diagnosis and staging procedures, definitive pathology report, first-line therapy, and clinical outcomes. Biological data included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), BM analysis, and cerebrospinal fluid (CSF) analysis. Imaging reports from computed-tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computerized tomography (18FDG-PET/CT) were collected.

Staging of IVL was done according to the Ann Arbor classification. CNS was considered involved if a patient presented with neurological symptoms supported by spinal tap analysis or CNS imaging.[14]

Response assessment was performed according to the revised RECIST guideline (version 1.1) as complete response (CR), partial response (PR) (including stabilization), or no response (including progression). The RECIST guideline is not routinely used to monitor patients with IVL because this disease is difficultly evaluated by imaging. However, we used this guideline to evaluate the course of the disease since these criteria were used by our patients' clinicians. CR was defined as the disappearance of clinical, biological, and imaging findings. PR was defined as the persistence of clinical, biological, and imaging findings despite an improvement, and no response was defined as the absence of response or as the progression of the disease. However, none of our patients had flow cytometry on cerebrospinal fluid (CSF).

2.2. Literature review of case series

We searched PubMed and Medline databases using the following terms: "intravascular lymphoma," "intravascular lymphomatosis," "angio-endotheliotropic lymphoma," "angiotropic large cell lymphoma," and "angioendotheliomatosis proliferans systemica" and restricted to English and French articles only. No prospective studies were retrieved. Reports with clinical, radiological, and histological data were included.

2.3. Statistical analysis

Descriptive statistics included the median values for continuous variables, and the percentages for categorical variables. Kruskal–Wallis test was used to compare continuous data, while Fischer exact test was used to compare frequency data between the 3 subgroups.[22,23] Our subgroups were based on immunophenotypic features, as reported in the literature ($CD5^+$ or $CD5^-CD10^+$; $CD5^-CD10^-$; $CD5^+CD10^-$).[6,12,24–28] Duration of follow-up was calculated from the beginning of symptoms to last clinical follow-up or death from any cause. Overall survival (OS) was calculated from the time of IVL diagnosis to last follow-up or death from any cause. Event-free survival (EFS) was calculated from the time of IVL treatment to relapse, progression, last follow-up, or death from any cause. Patient survival data was analyzed using Kaplan–Meier method and comparison analysis of OS and EFS between the 3 subgroups was done using log-rank test.[29,30] All data were analyzed with statistical software (SPSS-version 20) and the value of significance for P was prospectively set at 0.05.

3. Results

Twenty-nine patients were identified: 26 were Caucasian and 3 were Asian. A total of 4020 medical files were reviewed and 71 cases were falsely coded as IVL.

3.1. Clinical presentation and imaging

The median age was 66.7 years (range 47.2–90.8), with a M:F ratio of 1.23.

One case of IVL was associated with a previous malignancy (diffuse large B-cell lymphoma diagnosed 4 years prior IVL); when IVL diagnosis was made, this patient had achieved complete remission of his previous malignancy. Another case was associated with an Evans syndrome treated with long-term corticosteroid therapy plus splenectomy and another case occurred 10 years after liver transplant.

Patients presented with nonspecific symptoms, a significant deterioration in general status (ECOG-PS ≥2 in 100% of patients), fever (75%), and weight loss (69) (Table 1). All patients had stage IV-B IVL and 7 patients had lymph node enlargement.

Neurological signs and symptoms were present in 22 (75.9%) patients at diagnosis (Table 1). Neurological symptoms were heterogeneous, including confusion (48), weakness (38%), balance disorder (35%), memory loss (31%), headache (21%), convulsion (21%), paresis (21%), psychomotor disorders (17%), altered level of consciousness (14%), dysarthria (14%), paresthesia (14%), urinary/faecal incontinence (14%), cognitive impairment (10%), aphasia (10%), hypoesthesia (10%), vertigo (7%), and muscle spasms (7%). Neurological symptoms were the only presenting symptoms in 12 cases. Neuroimaging confirmed CNS and/or spinal cord involvement in 12 of the 22 cases Radiological findings were not specific and included multiple hypodensities of the cerebral white matter (n = 10), cerebral oedema (n = 3), abnormal intracerebral diffuse pseudonodular signal suspicious for vasculitis or IVL localization (n = 3), thickening of the pituitary stalk (n = 1), extensive hyperintense dorsal intramedullary signal (n = 3) and conus medullaris edema and demyelination (n=1). Among the 7 patients with no neurological signs or symptoms, neuroimaging and lumbar puncture (LP) were performed among 5 of them and did not detect lymphoma (4 CNS imaging and 5 spinal tap).

Spinal tap analysis was performed in 22 patients, 17 of whom had neurological signs or symptoms. An elevation in the cerebrospinal fluid (CSF) protein (≥0.45 g/L) and glucose (≥4.5 mmol/L) was observed in 11 and 5 cases, respectively. In cases with neurological symptoms, these abnormalities were observed in 9 and 2 patients, respectively. Five of the 17 cases

Table 1

Clinical characteristics of patients in the entire series (n=29).

Phenotype	Total	$CD5^+$ or $CD5^-CD10^+$*	$CD5^-CD10^-$	$CD5^+CD10^-$	*P* value
No. of patients	29	1	5	9	–
Age at diagnosis, y					
Median	66.7	88.8	68.3	66	–
Range	47.2–90.8	–	49.4–75.7	61.6–68.67	
Older than 60	24 (82.8)	1 (100)	3 (60)	2 (22.2)	
Sex, male	16 (55.2)	1 (100)	2 (40)	5 (55.6)	1.00
Performance status ≥ 2	29 (100)	1 (100)	5 (100)	9 (100)	–
Serum LDH (≥250 UI/L)	28 (97)	1 (100)	5 (100)	8 (88.9)	1.00
Stage IV	29 (100)	1 (100)	5 (100)	9 (100)	–
IPI					
Low	0	0	0	0	–
Low-intermediate	0	0	0	0	–
High-intermediate	0	0	0	0	–
High	29 (100)	1 (100)	5 (100)	9 (100)	
B symptoms present	29 (100)	1 (100)	5 (100)	9 (100)	–
Hepatomegaly	4 (13.8)	0	1 (20)	3 (33.3)	1.00
Splenomegaly	13 (44.8)	0	2 (40)	7 (77.8)	0.16
Respiratory signs and symptoms	8 (27.6)	0	2 (40)	3 (33.3)	1.00
Neurologic signs and symptoms	22 (75.9)	1 (100)	3 (60)	6 (66.7)	1.00
Skin lesions	5 (17.2)	1 (100)	0	0	0.07
Hemophagocytosis in BM	2 (6.9)	0	0	2 (22.2)	0.57
Tumor cells in BM	8 (27.6)	0	1 (20)	4 (44.4)	0.72
Anemia (<12 g/dL)	27 (93.1)	1 (100)	4 (80)	9 (100)	0.40
Leukopenia ($<4 \times 10^9$/L)	18 (62.1)	1 (100)	2 (40)	5 (55.6)	0.63
Thrombocytopenia ($<150 \times 10^9$/l)	15 (51.7)	0	1 (20)	7 (77.8)	0.05
Albumin level (<36 g/L)	23/28 (82.1)	0	4/4 (100)	6 (66.7)	0.18
Bilirubin level (≥15 umol/L)	9/28 (32.1)	0	1/4 (25)	6 (66.7)	0.27
Creatinine level (≥15 mg/L)	8 (27.6)†	0	2 (40)	2 (22.2)	0.69
ESR level (≥ 15 mm/h)	23/25 (92)	0	3/4 (75)	7/7 (100)	0.06
CRP level (≥50 mg/L)	24/25 (96)	1 (100)	3/4 (75)	7/7 (100)	0.42
Ferritin (≥ 375 ug/L)	15/18 (83.3)	0	1/2 (50)	6/7 (85.7)	0.18
Anthracycline-based chemotherapy	18 (62.1)	0	2 (40)	9 (100)	*0.01*
Overall survival (days)	135‡	135	10	–	0.20
Event-free survival at 3 yo (%)	64.2	–§	50	62.2	0.68

Values before and after slash indicate numbers of positive and evaluable patients, respectively. In the absence of a slash, all patients are evaluable. Values in parentheses are percentages. *P* values less than 0.05 are italicized.

BM=bone marrow, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, IPI=international prognostic index, LDH=lactate dehydrogenase.

* Including $CD5^-CD10^+$ (n=0) and $CD5^+CD10^+$ (n=1) types.

† One case had chronic renal insufficiency.

‡ In the entire series (n=29).

§ The patient did not receive chemotherapy.

with CNS involvement who underwent a LP had cells in the CSF suspected, but not confirmed, as malignant.

Five patients (17.2%) presented cutaneous lesions at diagnosis (Table 1). All these patients presented with neurological symptoms. Therefore, none of these had the "cutaneous variant" reported with isolated cutaneous involvement. Cutaneous manifestations were nonspecific: painful indurated erythema (n=2), purplish plaques (n=2), painful nodules (n=2), annular plaques (n=2), pruritus (n=2), angioectasias (n=1), panniculitis (n=1), purpura (n=1), and petechiae (n=1). The lesions were most commonly located on the legs, chest, and back.

Pulmonary features were present in 8 patients (27.6%), which included dry cough (n=5), dyspnea (n=7), and acute respiratory distress syndrome (ARDS) (n=1) (Table 1). Pulmonary imaging showed pleural effusion (n=3), alveolar infiltration (n=2), diffuse ground glass shadow (n=2), and ARDS (n=1). Among patients with pulmonary symptoms, transthoracic echocardiogram (TTE) showed pulmonary arterial hypertension (PAH) in 1 case and diastolic dysfunction in 2 cases. The other patients had no cardiopulmonary abnormalities.

Seven (24.1%) patients presented gastrointestinal symptoms, including nausea/vomiting (n=3), abdominal pain (n=2), abdominal mass (n=1), and icterus (n=1). Abdominal imaging showed adrenal mass and/or adrenal hypermetabolism (n=6), renal mass with hydronephrosis (n=1), duodenal mass (n=1), abdominal panniculitis (n=1), hepatomegaly (n=4), and splenomegaly (n=13) (Table 1).

3.2. Immunohistopathological features

Diagnoses were made in vivo in 23 patients (79.3%). Nine of these were made via skin biopsy (39.1%), 4 via BM biopsy (17.4%), 4 via cerebral biopsy (17.4%), 3 via renal biopsy (13%), 1 via duodenal biopsy (4.3%), 1 via hepatic biopsy (4.3%), and 1 via retroperitoneal lymphadenopathy biopsy (4.3%). Among the 9 patients with skin biopsy, 4 were done in patients with no cutaneous symptoms. Skin biopsies were from thighs (56%), abdomen (33%), and abdomen plus thighs (11%). Among the 6 patients with a post-mortem diagnosis, 1 had IVL diagnosed based on a BM biopsy done in vivo (Table 2).

Biopsied tissue showed large lymphoid cells within vessel lumina and all of them shared a B-cell immunophenotype (Fig. 1). According to the pathological reports, 2 Caucasian cases (7.7%) had "Asian variant" IVL and 2 cases (6.9%) presented a concomitant minimal extravascular infiltration of neoplastic lymphocytes. The percentage of extravascular cells was not available. One of our cases (3.4%) presented a solid concomitant neoplasia (renal clear cell carcinoma).

Immunophenotype analysis was available for 28 patients (Table 3). CD20 was virtually expressed. The 3 IVL subgroups ($CD5^+$ or $CD5^-CD10^+$; $CD5^-CD10^-$; $CD5^+CD10^-$) were analyzed for outcomes and no significant difference in OS and EFS was observed (OS $P=0.20$; EFS $P=0.68$) (Table 1).

3.3. Laboratory findings

Anemia (<12 g/dL) was the most frequent cytopenia (93%), followed by leucopenia (<4 10^9/L) (62%) and thrombocytopenia (<150 10^9/L) (52%). Among the 15 patients with thrombocytopenia, 3 (20%) of them presented disseminated intravascular coagulopathy (DIC) and 6 (40%) of them presented bone marrow infiltration. Among these 6 cases, 2 presented with hepatosplenomegaly and 2 had splenomegaly without hepatic involvement. Serum lactate dehydrogenase (LDH) level was elevated in 28 patients (97%). Elevation in ESR and CRP was observed in 23 of 25 (92%) and 24 of 25 cases (96%), respectively. Ferritin was also elevated in 15 of 18 patients (83%). Altered hepatic, renal, or thyroid functional tests were observed in 21 of 28 (75%), 8 of 29 (28%), and 1 of 21 (5%), respectively.

Table 2

Diagnostic sites in the entire series (n=29).

	Entire series n (%)
In vivo diagnostic sites (n=24)*	
Skin	9 (38)
BM biopsy	5 (21)
Brain	4 (17)
Kidney	3 (12)
Duodenum	1 (4)
Liver	1 (4)
Retroperitoneal lymphadenopathy	1 (4)
Post-mortem diagnostic sites (n=5)	
Brain	1 (20)
Lung/liver/kidney	1 (20)
Thyroid/spleen/bladder	1 (20)
All organs	2 (40)

BM=bone marrow.
* One of the cases received post-mortem diagnosis based on an in vivo BM biopsy.

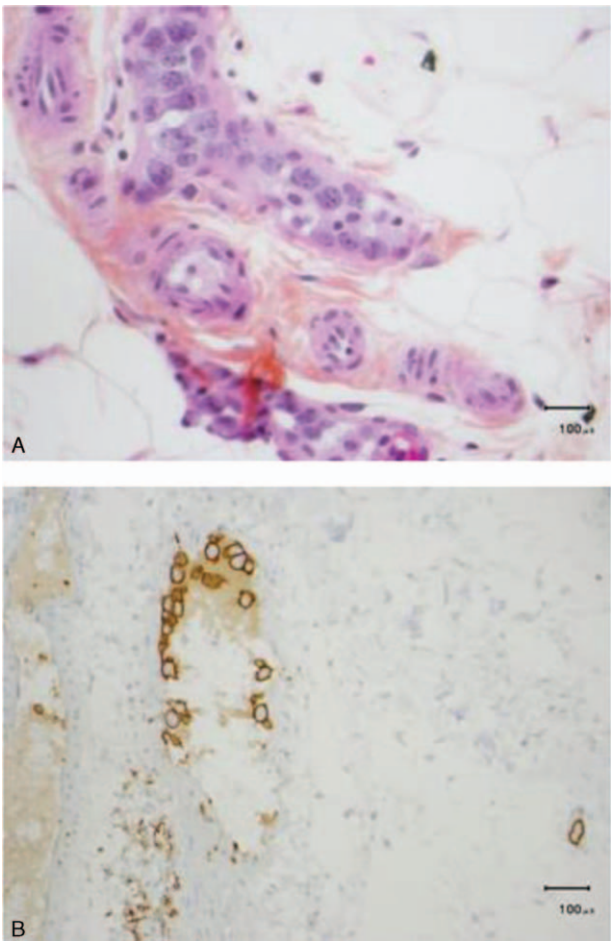

Figure 1. Pictures of a cutaneous biopsy of a large B-cell intravascular lymphoma case. A, Hematoxylin and eosin stain: large, atypical lymphomatous cells fill small blood vessels. B, Immunoperoxydase technique on paraffin section: the large cells in the small vessels are CD20+.

Table 3

Immunophenotypic features and EBV status of 29 cases with IVL.

	Entire series	$CD5^+$	$CD5^-$
No. of patients	29	13	5
CD20	28/28 (100)	13/13 (100)	5/5 (100)
CD10	1/18 (6)	1/10 (10)	0/5 (0)
CD3	12/22 (55)	7/11 (64)	2/5 (40)
MUM-1	17/18 (94)	12/12 (100)	4/5 (80)
Bcl-6	17/19 (89)	10/11 (91)	4/5 (80)
Bcl-2	16/19 (84)	9/11 (82)	5/5 (100)
High Ki-67 (>90%)	14/14 (10)	7/7 (100)	4/4 (100)
EBV	2/5 (40)	1/4 (25)	–
HHV8	0/2 (0)	0/2 (0)	–

Values before and after slash indicate numbers of positive and evaluable patients, respectively. In the absence of a slash, all patients are evaluable. Values in parentheses are percentages.
EBV = Epstein–Barr virus.

Among patients with abnormal liver function tests, 4 had hepatic involvement confirmed via in vivo biopsy (n = 1) or autopsy (n = 3). Infectious diseases were assessed in 18 patients and only 1 of them had an infection (oropharyngeal candidiasis).

3.4. Differential diagnosis

Most frequent diagnoses proposed before IVL diagnoses were: transitory ischemic attack (5 patients (17%)), sepsis (6 patients (21%)), temporal arteritis (8 patients (28%)), vasculitis (11 patients (38%)), and non-Hodgkin lymphoma (14 patients (48%)) (Table 4).

3.5. Treatments

Before IVL diagnosis was made, 22 patients received empiric treatment: corticosteroids (n = 18), antibiotics (n = 15), and blood transfusion (n = 11).

Among the 29 patients, 11 did not receive chemotherapy and were treated exclusively with palliative intent. Eighteen cases received first-line chemotherapy: either R-CHOP [rituxan, cyclophosphamide, hydroxyadriamycine, oncovin, prednisone] (n = 17) or CHOP regimen (n = 1). One of the patients treated with R-CHOP received ESHAP regimen [etoposide, methylprednisone, cytarabine, cisplatin] as a second-line chemotherapy, R-ICE regimen [rituxan, ifosfamide, etoposide, carboplatin] and R-GEMOX regimen [rituxan, gemcitabine, oxaliplatin] as third and fourth-line chemotherapy, respectively.

Ten of the 18 patients treated with chemotherapy received a therapy targeting the central nervous system (CNS): 6 received intrathecal methotrexate (ITMTX) and 4 received high-dose methotrexate (HDMTX). HDMTX was defined as MTX dose between 1 and 3 g/m^2.

None of the patients received hematopoietic stem cell transplantation (HSCT).

3.6. Outcomes

At the time of analysis, 15 patients completed first-line therapy. We observed 8 (53%) complete remission (CR), 3 (20%) partial remission (PR), and 4 stable or progressive disease.

With a median follow-up of 328 days (CI 181–474), OS at 3 years was 42.7% and 47.4% for the entire cohort and for the cases with in vivo diagnosis, respectively. Twelve patients were alive at the time of collecting data: 8 with CR, 1 with PR, and 3 receiving first-line chemotherapy (Table 5). EFS at 3 years was 64.2% (Fig. 2).

4. Discussion

This comprehensive review on the clinical presentation and management of IVL represents the largest series of IVL in North America to our knowledge.

We present a high prevalence of diagnosis made in vivo (79%), possibly reflecting a better recognition of this condition, as seen in recent literature.[9–13]

Our study depicts IVL as the aggressive condition already reported.[9–12,14] Clinical presentation is heterogeneous, ranging from unspecified symptoms to rapidly progressive manifestations of multiple organ dysfunction syndrome (MODS). Constitutional and nonspecific symptoms were present in all our cases

Table 4

Differential diagnosis in the entire series (n = 29).

Differential diagnosis	Entire series n (%)	Type of disease
NHL	14 (48)	Constitutional symptoms with abnormal blood count ± lymphadenopathy, splenomegaly or tumor at imaging (n = 14)
Vasculitis	11 (38)	Constitutional symptoms with cutaneous, muscular or neurological symptoms (n = 11)
Temporal arteritis	8 (28)	Fever with deterioration in functional status (n = 8)
Sepsis	6 (21)	Fever and shock (n = 2)
		Fever and DIC (n = 2)
		Fever, tachycardia and rapidly progressive confusion (n = 2)
TIA	5 (17)	Neurological symptoms, mainly headaches (n = 1)
		Neurological symptoms with abnormal intracerebral diffuse pseudonodular signal and multiple hypodensities of the cerebral white matter (n = 1)
Leukemia	4 (14)	Neurological symptoms with cerebral oedema and multiple hypodensities of the cerebral white matter (n = 3)
		Constitutional symptoms with abnormal blood count (n = 4)
Sarcoidosis	3 (10)	Neurological symptoms with thickening of the pituitary stalk (n = 1)
		Neurological symptoms with multiple hypodensities of the cerebral white matter plus extensive hyperintense dorsal intramedullary signal (n = 1)
		Constitutional symptoms with renal mass and lymphadenopathies (n = 1)
Multiple sclerosis	2 (7)	Neurological symptoms and cerebral oedema, abnormal intracerebral diffuse pseudonodular signal plus extensive hyperintense dorsal intramedullary signal (n = 1)
		Neurological symptoms with abnormal intracerebral diffuse pseudonodular signal (n = 1)

Values in parentheses are percentages.
DIC = disseminated intravascular coagulation, NHL = non-Hodgkin lymphoma, TIA = transitory ischemic attack.

Table 5

Causes of death in the entire series (n = 17).

	Entire series n (%)
Deterioration in functional status and/or progression of pancytopenia	6 (35)
Progression of neurological involvement	4 (23)
ARDS	1 (6)
DIC	1 (6)
MODS	1 (6)
Shock	
Multifactorial	2 (12)
Septic	1 (6)
GI obstruction	1 (6)

Values in parentheses are percentages.

ARDS = acute respiratory distress syndrome, DIC = disseminated intravascular coagulation, GI = gastrointestinal, MODS = multiple organ dysfunction syndrome.

contributing to the typical delay in diagnosis associated with IVL.[9–12,14]

Our series mainly report classical form of IVL with neurological and skin involvement and rare hemophagocytosis (7%).[9,10] Unlike European case series, none of our cases had the "cutaneous variant" of IVL.[9,10,31] This trend is also seen in Canadian literature, where most of the IVL case reports describe neurological involvement as the main clinical presentation instead of cutaneous symptoms and the "cutaneous variant" of IVL.[18–21] This leads us to believe that the French Canadian "classical" IVL, more focused on neurological abnormalities, may be different from the one seen in Europe. Neurological symptoms, which were the dominant features, were heterogeneous and were the unique presenting symptoms in 12 of our cases. Neuroimaging did not detect brain lesions in 45% of the patients with neurological symptoms and none of our cases without neurological symptoms had a positive neuroimaging. Thus, prompt CNS imaging in patients with CNS symptoms is recommended.[18–21,32–34] Seventeen cases with neurological complaints had a lumbar puncture and, among them, elevation in CSF protein and glucose were seen in 53% and 12%, respectively. Flow cytometry offers a higher sensitivity to detect lymphoma infiltration and could facilitate CNS staging. Further analysis is warranted to better understand the role of flow cytometry in IVL.

Regarding previous studies, bone marrow is usually spared in "classical" IVL.[16,35] However, bone marrow involvement was noted in 28% of our cohort (n = 8), which is similar to recent European case series.[9,10] Among the 5 patients who presented only persistent constitutional symptoms and had diagnosis based on BM biopsy, the bone marrow was the only detectable site of disease in 4 of them (80%). According to these findings, bone marrow biopsy should be done in IVL cases for diagnosis and staging.[9,10] Moreover, similarly to the reported observations in recent studies on minimal extravascular infiltration in IVL, we observed extravascular involvement in 7% of our cohort.[10,36–38]

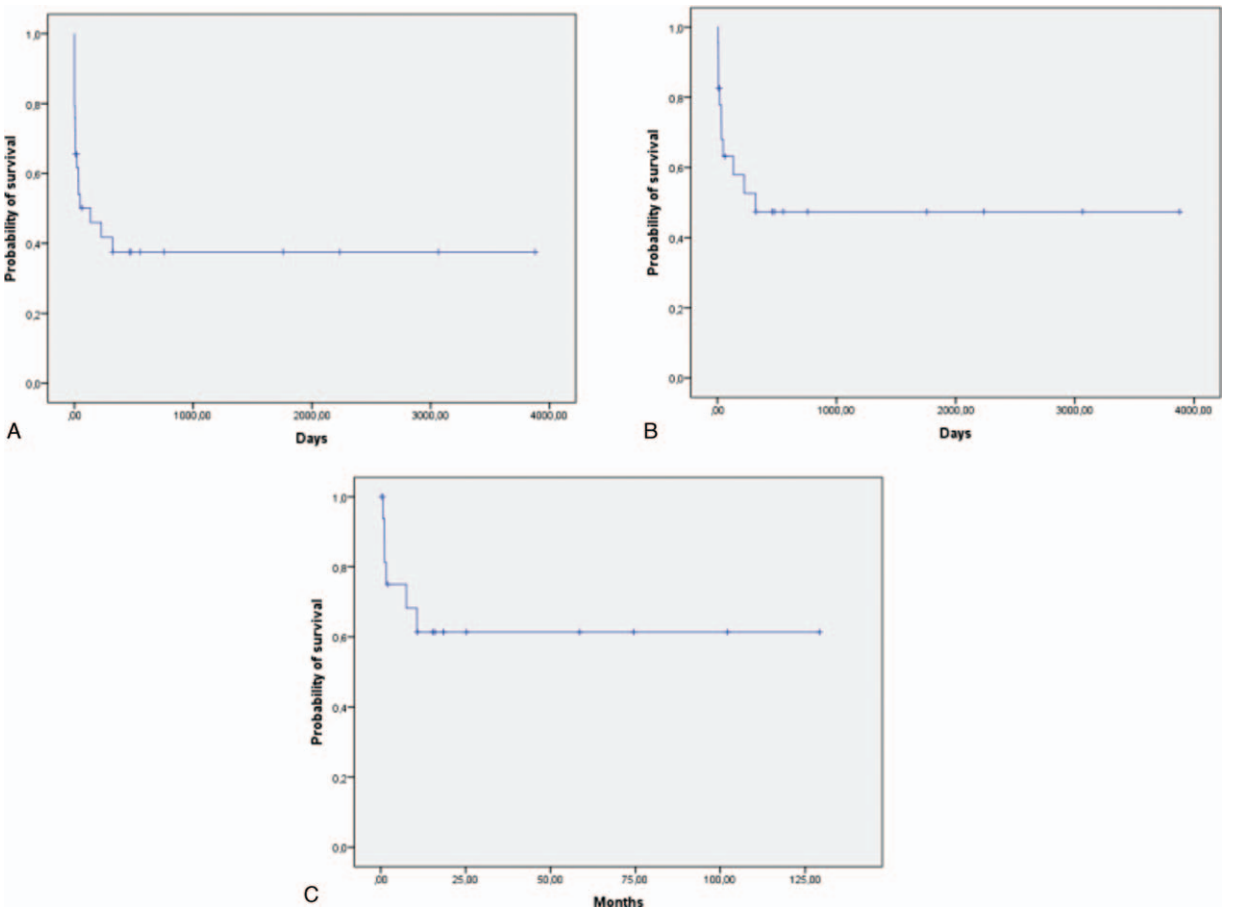

Figure 2. A, Overall survival (OS) curve for the entire case series (n = 29). B, OS curve for patients with in vivo diagnosis (n = 23). C, Event-free survival (EFS) for patients treated with chemotherapy (n = 15).

Initial presentation of IVL seems to differ between non-Asian and Asian countries. "Classical" IVL, mainly reported in Europe, is characterized by cutaneous and/or neurological involvement while "Asian variant" IVL, mainly reported in Asia, is characterized by hemophagocytic syndrome, BM involvement, fever, hepatosplenomegaly, and/or thrombocytopenia. In our cohort, 2 Caucasian patients (7.7%) presented "Asian variant" IVL; this observation is not unusual, as cases of "classical" IVL have been reported in Asians and "Asian variant" IVL has been reported in Europeans and Africans.[3,39–44] This leads us to believe that IVL nomenclature should use "classical IVL" and "IVL associated with hemophagocytic syndrome," instead of "European IVL" and "Asian variant" IVL.

Considering our case series, patients with a diagnosis of IVL should be considered as having an advanced stage disease at initial presentation and should be treated promptly with an intensive combined chemotherapy. Anthracycline-based chemotherapy should be used in patients with IVL to improve outcomes.[10,12,14,28,38,45–51] In our case series, all 18 patients treated with chemotherapy received an anthracycline-based treatment as first-line regimen and 53% of them achieved CR, which is consistent with reported outcomes.[9,10,12,13] None of the patient received high-dose therapy followed by autologous stem cell transplant. OS at 3 years was 42.7% for the entire cohort and the EFS at 3 years was 64.2% which is consistent with other reported series.

Although our conclusions are based on a significant number of cases, they should be interpreted with caution. First, this is a retrospective, and not a prospective, multicenter series. Second, some patient data was missing. Third, there was no reexamination of the investigation results or of specialists' conclusions. Fourth, the definition of CNS involvement included arbitrary aspects; in this study, all the patients with neurological symptoms confirmed by either physical examination, laboratory findings, or image findings were considered as having CNS involvement. Finally, some cases were likely missed as not all Hematology-Oncology centers from the province of Québec participated in our study.

5. Conclusion

Unlike European studies on "classical" IVL, our study showed that the French Canadian presentation of this subtype of IVL is more frequently observed with neurological rather than cutaneous involvement. Since 2 of our Caucasian patients presented "Asian variant" IVL and that the clinical presentations of IVL can be seen elsewhere in the world, like in Canada, we suggest that the IVL nomenclature should use "classical" IVL and "IVL associated with hemophagocytic syndrome," instead of "European" IVL and "Asian variant" IVL. Finally, an early diagnosis is of primary importance since almost a quarter of patients receive a post-mortem diagnosis. A prompt diagnosis allows the introduction of an early treatment, associated with a CR in 53% of patients. This is considerable for a disease that was until recently described as incurable.

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