

# Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'<sup>1</sup>

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## Summary

Despite its recognition as a distinct, extremely rare entity, no large studies of intravascular lymphoma (IVL) have been reported. The clinico-pathological characteristics of 38 human immunodeficiency virus-negative patients with IVL diagnosed in Western countries were reviewed to better delineate clinical presentation, clinical variants, natural history and optimal therapy. The IVL is an aggressive and usually disseminated disease (Ann Arbor stage IV in 68% of cases) that predominantly affects elderly patients (median age 70 years, range: 34–90; male:female ratio 0.9), resulting in poor Eastern Cooperative Oncology Group Performance Status (ECOG-PS >1 in 61%), B symptoms (55%), anaemia (63%) and high serum lactate dehydrogenase level (86%). The brain and skin are the most common sites of disease. In contrast to previous reports, hepatosplenic involvement (26%) and bone marrow infiltration (32%) were found to be common features in IVL, while nodal disease was confirmed as rare (11% of cases). Patients with disease limited to the skin ('cutaneous variant'; 26% of cases) were invariably females with a normal platelet count, and exhibited a significantly better outcome than the remaining patients, which deserves further investigation. Overall survival was usually poor; however, the early use of intensive therapies could improve

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outcome in young patients with unfavourable features. ECOG-PS >1, 'cutaneous variant', stage I and chemotherapy use were independently associated with improved survival.

**Keywords:** extranodal lymphoma, angiotropic lymphoma, intravascular lymphoma, cutaneous lymphoma, central nervous system lymphomas.

Intravascular lymphoma (IVL) or 'angiotropic lymphoma' (formerly known as 'malignant angioendotheliomatosis' Bhawan, 1987) is a rare entity characterized by exclusive or predominant growth of neoplastic cells within the lumina of blood vessels (Bhawan *et al*, 1985; Wrotnowski *et al*, 1985; Carroll *et al*, 1986). This disorder has been recently recognized as a subtype of diffuse large B-cell lymphoma in the World Health Organization (WHO) Classification (Gatter & Warnke, 2001), although rare forms with a T-cell phenotype do exist (Chen *et al*, 1998). The understanding of IVL is very limited considering that literature on this malignancy is almost exclusively represented by case reports, cumulative reviews and occasional studies that do not exceed 10–15 patients (Stroup *et al*, 1990; Glass *et al*, 1993; DiGiuseppe *et al*, 1994).

Most clinical and biological properties of IVL are largely unknown. The heterogeneity of clinical presentation and the lack of diagnostic algorithms may explain why approximately half of IVL cases are diagnosed only after autopsy (Domizio *et al*, 1989) and many of the antemortem diagnoses are made incidentally in biopsies performed for different reasons. Accordingly, clinical syndromes and predictors of survival have not been defined in IVL. The course of this malignancy is generally rapidly progressive and ultimately fatal, with the exception of some patients that achieve durable remission after chemotherapy and rare cases of untreated long-term survivors (DiGiuseppe *et al*, 1994; Bogomolski-Yahalom *et al*, 1998).

This report describes presenting symptoms, clinical variants, course, prognostic factors, therapeutic management and outcome of the largest reported series ( $n = 38$ ) of IVL diagnosed in Western Countries, including either *in vivo* and postmortem diagnosed cases. The peculiar clinical features and behaviour of an hitherto not described 'cutaneous variant' of IVL are analysed.

## Patients and methods

### Study group

Twenty-two centres affiliated with the International Extranodal Lymphoma Study Group (IELSG) provided data on patient characteristics, diagnosis, sites of disease, stage, treatment and outcome of 38 human immunodeficiency virus (HIV)-negative patients with an *in vivo* or postmortem pathological diagnosis of IVL between 1985 and 2003. WHO diagnostic criteria were used (Gatter & Warnke, 2001). Diagnosis was established *in vivo* in 30 (79%) patients and postmortem in eight (21%); it

was incidental in four patients referred for surgical resection of benign prostate hyperplasia ( $n = 2$ ), a cervical polyp or renal cancer. Staging work-up included physical examination, complete biochemical profile, whole-body computerized tomography (CT) scan, and bone marrow aspirate and biopsy. Disease stage was defined according to the Ann Arbor staging system (Carbone *et al*, 1971). Some procedures, such as CT or magnetic resonance imaging (MRI) of the brain, cerebrospinal fluid (CSF) cytology examination, gastroscopy, abdominal ultrasound or hysteroscopy, were indicated according to presenting features in individual cases. The study conformed to the tenets of the Declaration of Helsinki. Some preliminary results have been published (Ferreri *et al*, 2002a,b).

### Statistical considerations

Correlations among variables were assessed by Spearman test. Survival curves were generated by the Kaplan–Meier method. Overall survival (OS) was calculated from the date of pathological 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. Impact on survival of clinical and therapeutic variables was evaluated using the log-rank test. The independent prognostic value of variables was analysed using the Cox model. All the probability values were two-sided, with an overall significance level of 0.05. There was no correction for multiple comparisons. Analyses were carried out using the STATISTICA 4.0 statistical package for Windows (Statsoft Inc., 1993, Tulsa, OK, USA).

## Results

### Clinical presentation

The median age of the 38 patients was 70 years (range: 34–90), with a male/female ratio of 0.9. IVL was associated with a previous or concomitant malignancy in six cases (16%): four patients had a previous neoplasia [colon cancer, prostate cancer, breast cancer and marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)-type of the stomach] diagnosed 4–5 years before IVL; IVL was concomitant to other tumours in two patients (renal cancer and diffuse large B-cell lymphoma of salivary gland).

Patients usually presented non-specific symptoms with a remarkable deterioration in the Eastern Cooperative Oncology

Table I. Presenting symptoms.

	Exclusive symptoms	Associated symptoms
Systemic symptoms ( <i>n</i> = 21; 55%)	9 (24)	12 (32)
Fever	3 (8)	4 (11)
Fever + weight loss ± night sweats	5 (13)	4 (11)
Fever + night sweats	0 (0)	1 (3)
Weight loss	1 (3)	3 (8)
Cutaneous lesions	10 (26)*	5 (13)
Neurological symptoms	5 (13)	8 (21)
Pain	1 (3)	7 (18)
Fatigue	0 (0)	6 (16)
Gastrointestinal symptoms	0 (0)	2 (5)
Urinary symptoms	1 (3)	2 (5)
Cardiac dysfunction	0 (0)	2 (5)
Oedema	0 (0)	2 (5)
Dyspnoea	0 (0)	1 (3)

\*The 10 patients with disease exclusively limited to the skin constituted the subgroup of patients with the 'cutaneous variant' of intravascular lymphoma (IVL).

Values in parentheses expressed as percentage.

Group (ECOG) performance status (PS), which was  $\geq 1$  in 36 cases (95%). Twenty-one patients (55%) had systemic symptoms (Table I), mainly fever, which was present in 17 cases (45%). Fever was associated with other B symptoms in 10 cases, while four patients experienced weight loss without fever. B symptoms were the only presenting symptom in nine patients (24%).

Cutaneous lesions were the dominant presenting feature in 15 (39%) cases (Table I). Lesions encompassed a widespread morphology and distribution, including painful indurate

erythematous eruption, poorly circumscribed violaceous plaques, swelling overlying skin 'peau d'orange', cellulitis, large solitary plaques, painful blue-red palpable nodular discolorations, tumour, ulcerated nodules, small red palpable spots, and erythematous and desquamative plaques. Lesions were more commonly situated in upper arms, thighs and legs, lower abdomen, breast and submammary region. Cutaneous lesions were single in four cases and multiple in 11. They were the only site of involvement in 10 cases, but were associated with other symptoms, mostly neurological and B symptoms, in five cases. Standard lymphoma staging procedures demonstrated further sites of disease in all these five patients, with the involved organs being liver, central nervous system (CNS), marrow, and/or spleen. The 10 patients whose disease was exclusively limited to the skin constituted the subgroup of patients with a 'cutaneous variant' of IVL.

Thirteen patients (34%) presented with neurological symptoms at diagnosis (five of them were diagnosed at autopsy). These symptoms were extremely heterogeneous, including sensory and motor deficits, meningoradiculitis, paresthesias, hypostenia, aphasia, dysarthria, hemiparesis, seizures, myoclonus, transient visual loss, vertigo, sensory neuropathy and altered conscious state. They were the unique presenting symptoms in five cases (Table I). Neuroimaging confirmed CNS involvement in four of the eight patients with neurological symptoms and *in vivo* diagnosis of IVL; in two cases CNS staging was negative although neoplastic infiltration was detected at autopsy a few weeks thereafter. Neuroimaging disclosed the presence of brain lesions in two additional patients without neurological symptoms at diagnosis.

Pain, mostly associated with cutaneous or abdominal (renal or adrenal) masses, and fatigue were two common presenting symptoms, affecting more than one-third of patients (Table I).

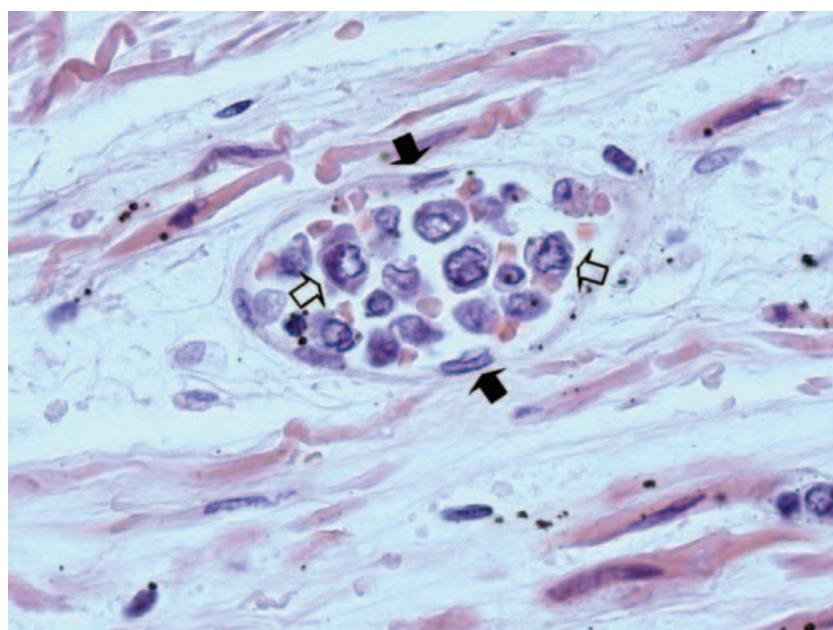


Fig 1. Intravascular lymphoma of the intestinal wall (haematoxylin and eosin). Large neoplastic cells (open arrows) were detected in a blood vessel lumen (endothelial cells; black arrows).

### Histopathological features

All cases showed large lymphoid cells within vessel lumina (Fig 1). Neoplastic lymphocytes showed large nuclei with one or more nucleoli and scant cytoplasm. All cases but one (T cell) shared a B-cell immunophenotype. Concomitant extravascular infiltrates of neoplastic lymphocytes were observed in four (11%) cases. A more accurate analysis of histopathological and immunophenotypic features will be performed in a forthcoming study.

### Stage and sites of disease

Among the 30 patients with an *in vivo* diagnosis of IVL, the Ann Arbor disease stage was I<sub>E</sub> in 12 (40%) cases and IV in 18 (60%). Stage IV disease was present in 10 patients with systemic disease after staging completion, in seven patients with multiple cutaneous lesions and negative staging at other sites, and in one patient with bone marrow infiltration as the sole site of disease (Table II). After diagnostic biopsy, standard staging work-up for lymphomas detected the involvement of bone marrow ( $n = 8$ ), CNS ( $n = 4$ ), spleen ( $n = 7$ ), liver ( $n = 6$ ), stomach ( $n = 1$ ), prostate ( $n = 1$ ), adrenal gland ( $n = 1$ ) and/or retroperitoneal lymph nodes ( $n = 2$ ). The limitations of standard lymphoma staging procedures in IVL patients were observed in two cases of early death, where a short-time period occurred between diagnosis and autopsy. In fact, these cases were considered as having stage I disease after conventional staging procedures, while the autopsy, performed

Table II. Sites of disease.

Involved organs	One organ	Multiple organs
Skin		
Single lesion	3 (8)	1 (3)
Multiple lesions	7 (18)*	4 (11)
CNS	2 (5)	13 (34)
Liver		10 (26)
Spleen		10 (26)
Bone marrow	1 (3)*	11 (29)
Peripheral blood smear		2 (5)
Lymph nodes		4 (11)
Endocrine glands		6 (16)
Lung	1 (3)	6 (16)
Heart		4 (11)
Gastrointestinal tract		3 (8)
Gallbladder	1 (3)	
Prostate	2 (5)	4 (11)
Kidney	2 (5)	6 (16)
Urinary bladder		3 (8)
Uterus	2 (5)	1 (3)

\*According to the Ann Arbor staging system, multiple cutaneous lesions and bone marrow infiltration were considered as stage-IV disease.

CNS, central nervous system.

Values in parentheses expressed as percentage.

2–7 weeks later, showed the presence of neoplastic cells in the vessels of several additional organs. Disseminated disease (stage IV) was reported in all autopsied cases.

The most commonly involved organs were the skin, CNS, bone marrow, liver and spleen (Table II). Cutaneous involvement was observed in 15 (39%) patients, in association with multiple organs in five. CNS lesions were detected in 15 (39%) patients, mainly within the context of multiorgan infiltration. Simultaneous liver, spleen and marrow involvement was observed in eight patients (21%). Overall, bone marrow biopsies were positive in 12 cases (32%); in one of them, bone marrow was the sole site of disease (stage IV). Peripheral blood smears were positive in two cases (5%) that were included in the subgroup with bone marrow infiltration. Lymph nodes were usually spared; two patients presented enlarged retroperitoneal lymph nodes at CT scan, which were not biopsied, and two additional patients had multiple retroperitoneal lymphadenopathy at autopsy. Involvement of lung, endocrine glands, kidney and prostate was common (Table II).

### Laboratory findings

Increased serum lactate dehydrogenase (LDH) and  $\beta$ 2-microglobulin levels were observed in 86% and 82% of assessed patients respectively (Table III). Anaemia (<12 g/dl) was the most frequent cytopenia (63%). Leucopenia (< $4 \times 10^9/l$ ) or thrombocytopenia (< $150 \times 10^9/l$ ) did not occur without anaemia. Eight of the 11 (73%) patients with thrombocytopenia had concomitant bone marrow infiltration and hepatosplenic involvement. All but one patient with marrow infiltration had anaemia or thrombocytopenia; patients with hepatic and/or splenic involvement ( $n = 12$ ) frequently had anaemia ( $n = 8$ ), leucopenia ( $n = 4$ ) or thrombocytopenia ( $n = 7$ ).

An elevated erythrocyte sedimentation rate (ESR) was present in 43% of cases. A monoclonal serum component was reported in five cases (14%): IgA ( $n = 2$ ), IgG ( $n = 2$ ) and IgM. Altered hepatic, renal or thyroid functional tests were observed in six cases (16%). In these cases, clinical staging or autopsy demonstrated lymphomatous infiltration of liver, kidneys or thyroid gland.

Laboratory findings in patients with the 'cutaneous variant' were similar to those of the other patients: elevated serum LDH in six (75%) of eight assessed patients, anaemia in five (50%) patients and raised ESR in four (44%) of nine assessed patients. Remarkably, patients with the 'cutaneous variant' did not have leucopenia, thrombocytopenia or monoclonal components.

### Correlations among variables

Interestingly, the 'cutaneous variant' of IVL was significantly correlated with gender, leucocyte and platelet counts and PS (Table IV). All patients with 'cutaneous variant' were females ( $P = 0.0004$ ) and had normal leucocyte ( $P = 0.03$ ) and platelet ( $P = 0.009$ ) counts; all but two of them had an

**Table III.** Laboratory findings in the entire series ( $n = 38$ ) and among patients with the 'cutaneous variant' of IVL ( $n = 10$ ).

Feature	Entire series		'Cutaneous variant'	
	N*	Cases (%)	N*	Cases (%)
Anaemia (<12 g/dl)	38	24 (63)	10	5 (50)
Leucopenia (< $4 \times 10^9/l$ )	38	9 (24)	10	0 (0)
Thrombocytopenia (< $150 \times 10^9/l$ )	38	11 (29)	10	0 (0)
High serum LDH	29	25 (86)	8	6 (75)
High serum $\beta$ 2-microglobulin	11	9 (82)	2	1 (50)
Elevated ESR	37	16 (43)	9	4 (44)
Hypoalbuminaemia (<36 g/l)	33	6 (18)	9	2 (22)
Monoclonal serum component	36	5 (14)	9	0 (0)

\*Assessable patients.

LDH, lactic dehydrogenase; ESR, erythrocyte sedimentation rate; IVL, intravascular lymphoma.

**Table IV.** Correlations among variables.

	Albuminaemia	Monoclonal component	Platelets ESR counts	Leucocytes counts	Haemoglobin level	Marrow infiltration	$\beta$ 2-microglobulin	LDH serum levels	B symptoms	Cutaneous variant	PS	Sex	
Age	-	$\Sigma$	-	-	-	-	-	-	-	-	$\Sigma$	-	$\Sigma$
Sex	-	-	-	S	-	-	-	-	-	-	S	-	$\Sigma$
PS	-	-	S	-	-	-	-	-	-	S	-	-	-
Cutaneous variant	-	-	S	S	-	S	S	-	S	-	-	-	-
Stage	-	-	-	-	-	S	-	S	-	-	-	-	-
B symptoms	-	-	-	S	S	-	-	S	-	-	-	-	-
Serum LDH	-	-	-	-	S	-	-	-	-	-	-	-	-
$\beta$ 2-microglobulin	-	-	-	-	S	-	-	-	-	-	-	-	-
Marrow infiltration	S	-	$\Sigma$	S	-	-	-	-	-	-	-	-	-
Haemoglobin level	$\Sigma$	-	$\Sigma$	S	S	-	-	-	-	-	-	-	-
Leucocyte count	-	-	-	-	-	-	-	-	-	-	-	-	-
Platelets count	-	-	S	-	-	-	-	-	-	-	-	-	-
ESR	S	-	-	-	-	-	-	-	-	-	-	-	-
Monoclonal component	-	-	-	-	-	-	-	-	-	-	-	-	-

S, significant correlation;  $\Sigma$ , near significant correlation ( $P = 0.05-0.075$ ); PS, Performance Status; LDH, lactic dehydrogenase; ESR, erythrocyte sedimentation rate.

**Table V.** Therapeutic management of 30 patients with *in vivo* diagnosed IVL.

Treatment	Number of patients	Type of disease
Chemotherapy	22	
Anthracycline-based*†	19	39-86 years old, all stages, all clinical variants
Alkylating-based†	3	One patient with cutaneous variant; two elderly patients
Other therapies		
Surgery alone	5	
Total resection	4	Elderly patients, PS = 3, stage I <sub>E</sub> , chemo refused
Partial resection	1	F/74 years old, PS = 4, stage IV <sub>E</sub> , early death
Radiotherapy	1	F/49 years old, single cutaneous lesion
Steroids	1	F/51 years old, multiple cutaneous lesions, LTF
None	1	F/90 years old, cervix biopsy, PS = 3, early death

\*Followed by high-dose chemotherapy supported by ASCT in two patients.

†Three patients with CNS involvement were also treated with intrathecal chemotherapy.

LTF, lost to follow-up; IVL, intravascular lymphoma; PS, Performance Status; ASCT, autologous stem cell transplantation; CNS, central nervous system.

ECOG-PS  $\leq 1$  ( $P = 0.001$ ). These patients were younger than the remainder of the series (median age: 59 vs. 72 years;  $P = 0.09$ ), and were less associated with B symptoms (30% vs. 65%;  $P = 0.04$ ) and bone marrow infiltration (0% vs. 43%;  $P = 0.01$ ).

Significantly positive correlations among some variables suggesting a more aggressive disease, such as advanced stage, high LDH serum level, B symptoms and anaemia, were observed (Table IV).

### Outcome

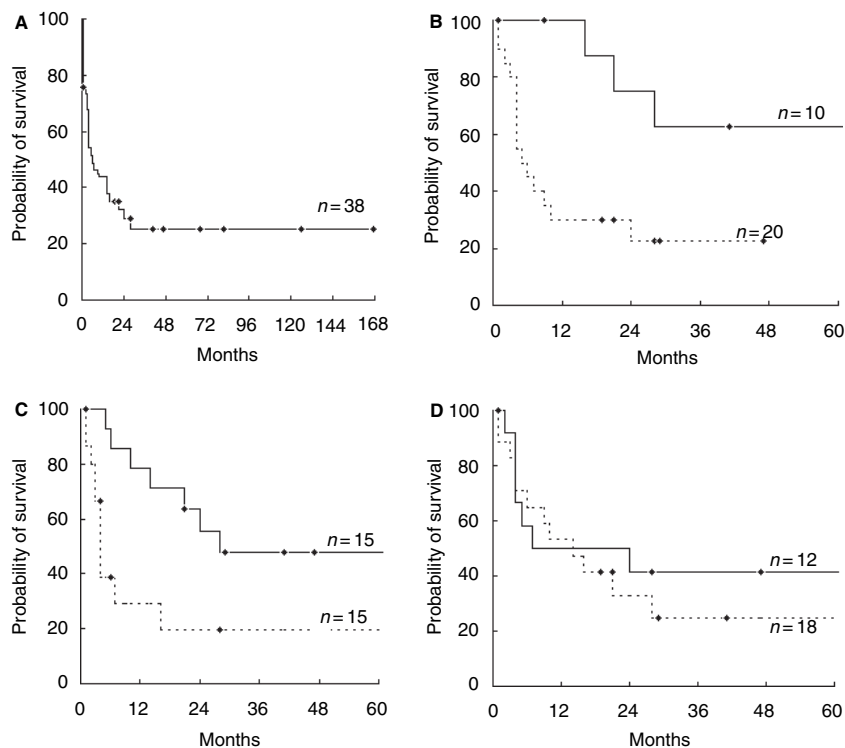
Therapeutic management of 30 patients with *in vivo* diagnosis is summarized in Table V. Twenty-two patients were treated with chemotherapy, which was anthracycline-based in 19 cases. Response after chemotherapy was complete (CR) in 10 cases and partial (PR) in three (ORR = 59%); seven patients showed progressive disease during therapy and two died of toxicity. Two women (43 and 52 years old), one with a single endometrial lesion and one with multiorgan disease, were treated with anthracycline-based chemotherapy [MACOP-B (methotrexate, adriamycin, cyclophosphamide, oncovin, prednisone, bleomycin) and CHOEP (cyclophosphamide, adriamycin, oncovin, prednisone, etoposide) regimens] followed by consolidation high-dose chemotherapy supported by autologous stem cell transplantation (ASCT); both are alive and relapse-free at 19 and 71 months from diagnosis.

Eight patients did not receive chemotherapy; five of them underwent surgical resection of tumour masses of kidney ( $n = 2$ ), prostate, gallbladder, and skin of the breast, and did not receive further treatment because of the presence of

concomitant renal cancer (limited disease), PS  $\geq 3$ , advanced age, or patient refusal. The patient with concomitant renal cancer died of unrelated causes, while lymphoma-free, at 24 months from diagnosis; the patient with a ulcerated cutaneous node of the breast is alive and relapse-free at 81 months of follow-up; the other three patients died of lymphoma within 5 months of diagnosis. The remaining three patients who did not receive chemotherapy were a 90-year-old woman who had concomitant end-stage renal failure; a 51-year-old woman with multiple cutaneous lesions, who was lost to follow-up after 1 month of steroid therapy; and a 49-year-old woman with a single cutaneous lesion who was treated with radiotherapy alone and was alive with no evidence of disease (NED) at 14 years from diagnosis.

Overall, at the completion of first-line treatment, 17 patients achieved an objective response (13 CR and four PR), nine patients experienced progression (PD) and four died of toxicity (TD). Among responders, eight subsequently experienced relapse, which invariably involved extranodal organs and, mostly, the primary site of disease. The median time to disease progression for the 30 patients with an *in vivo* diagnosis was 7 months (range: 1–81+), with a 3-year EFS of  $27 \pm 8\%$  (SD). All failures but one (66 months) occurred within the first year of follow-up.

Seven of 17 patients who experienced failure (i.e. progressive disease in nine and relapse in eight) received a salvage therapy: re-irradiation of a single cutaneous lesion in one patient with a 'cutaneous variant', who was alive and showed NED at 167 months from diagnosis; conventional chemotherapy in four cases (two PR, two PD), and high-dose chemotherapy supported by ASCT in two cases (PD, TD). Duration of the



**Fig 2.** (A) Overall survival (OS) curve for the entire series. (B) OS curves for patients with *in vivo* diagnosis of intravascular lymphoma (IVL) grouped according to the clinical variant. Patients with 'cutaneous variant' (solid line) survived longer than the rest (dotted line) ( $P = 0.007$ ). (C) OS curves for patients with an *in vivo* diagnosis of IVL grouped according to the Performance Status (PS). Patients with PS 0–1 (solid line) survived longer than others (dotted line) ( $P = 0.005$ ). (D) OS curves for patients with *in vivo* diagnosis of IVL grouped according to Ann Arbor stage. Patients with stage I<sub>E</sub> (solid line) survived longer than patients with stage IV disease (dotted line) ( $P = 0.05$ ).

second responses were 7, 8, 9+ and 19 months and 7 and 18 months respectively. Interestingly, a case of spontaneous regression of a cutaneous relapse was observed in a patient who is alive with NED at 10 years.

Eleven patients were alive (nine disease-free), at a median follow-up of 41 months (range: 1–167), with a 3-year OS of  $32 \pm 9\%$  for patients diagnosed during life and  $25 \pm 7\%$  for the entire series (Fig 2A). Of the surviving patients, six had the 'cutaneous variant', two had stage-I disease and three had stage-IV disease.

### Prognostic factors

Univariate analyses, which were limited to cases with *in vivo* diagnosis, showed that patients with the 'cutaneous variant' had significantly better survival (3-year OS:  $56 \pm 16\%$  vs.  $22 \pm 10\%$ ;  $P = 0.007$ ) (Fig 2B). Patients with good PS (ECOG  $\leq 1$ ) had a better survival (3-year OS:  $48 \pm 14\%$  vs.  $20 \pm 10\%$ ;  $P = 0.005$ ) (Fig 2C). Patients with stage I<sub>E</sub> disease also had better survival (3-year OS:  $42 \pm 14\%$  vs.  $24 \pm 11\%$ ;  $P = 0.05$ ) (Fig 2D).

Considering the distribution of the International Prognostic Index (IPI) on the entire series ( $n = 38$ ), the risk of death was low (score 0–1) in six cases, intermediate (score 2–3) in 16, and high (score 4–5) in 16 cases. The IPI analysis, when limited to the 30 cases with *in vivo* diagnosis, showed a near significant association with survival, with a 3-year OS of  $50 \pm 17\%$ ,  $35 \pm 14\%$  and  $20 \pm 13\%$ , respectively, for patients with low ( $n = 6$ ), intermediate ( $n = 14$ ) and high ( $n = 10$ ) risk ( $P = 0.09$ ).

Multivariate analysis on the entire series confirmed the independent prognostic value of 'cutaneous variant', PS, stage of disease and use of chemotherapy (Table VI). Similar results were obtained when analysis was limited to patients with *in vivo* diagnosed IVL (data not shown). When related variables were substituted with the IPI, clinical variant [ $P = 0.04$ ; odds ratio (OR), 0.27; 95% confidence interval (CI): 0.08–0.93], IPI ( $P = 0.003$ ; OR, 2.78; 95% CI: 1.46–5.30) and use of chemotherapy ( $P = 0.005$ ; OR, 0.24; 95% CI: 0.09–0.63) were independently associated with survival.

## Discussion

This study is the largest to date on clinical presentation forms, therapeutic management, outcome and prognostic factors in IVL patients from Western Countries. An important aspect of our series is the high prevalence of cases with *in vivo* diagnosis; this feature might reflect *per se*, in contrast to the past experience, an increasingly better recognition of IVL. Although our conclusions are determined from these representative numbers, they should be interpreted with caution considering the retrospective, multicentre nature of this series, which spans a 17-year period.

According to our cohort, IVL is an aggressive and disseminated malignancy that affects elderly patients, without gender prevalence, resulting in poor PS, B symptoms, anaemia and frequently elevated serum LDH levels. Clinical presentation is extremely heterogeneous, ranging from monosymptomatic forms, such as fever, pain or local symptoms, to the combination of B symptoms and rapidly progressing manifestations of multiorgan failure. B symptoms constituted the dominant presenting feature in a quarter of cases. In three cases, fever, which was remarkably more frequent in our series with respect to other extranodal aggressive lymphomas (45% vs. 25%), lead to histopathological examination of bone marrow, and ultimately the diagnosis of IVL.

The brain and skin were the most frequently involved organs; 68% of our patients had involvement of at least one of these organs. Cutaneous lesions were the main clinical presentation in 39% of our series; their aspect and distribution were greatly heterogeneous, being multiple in 80% of cases. In one-third of cases, cutaneous lesions were associated with other sites of disease, mainly bone marrow, CNS, liver, and spleen, while in the remaining two-thirds, the skin was the sole detectable site of disease (see below 'cutaneous variant'). Also, neurological symptoms were variable according to the affected region of the CNS (Beristain & Azzarelli, 2002). There are no pathognomonic neuro-radiological findings for IVL: ischaemic foci are the most common presentation pattern and vasculitis is the most common differential diagnosis (Song *et al*, 2002). Intriguingly, neuroimaging did not detect brain lesions in half

**Table VI.** Multivariate analysis: impact on overall survival on the entire series.

Variable	Subgroups	RR	95% CI	P-value
Age	Continuous variable	0.99	0.96–1.03	0.99
ECOG-PS	0–1 vs. 2–4	5.54	1.66–18.5	0.009
Clinical variant	Others vs. cutaneous	0.08	0.01–0.46	0.008
Stage	I vs. IV	4.72	1.31–17.1	0.02
B symptoms	No vs. yes	0.36	0.09–1.43	0.16
Serum LDH	Normal vs. elevated	0.99	0.08–11.7	0.99
Anaemia	No vs. yes	0.99	0.25–4.01	0.99
Chemotherapy	No vs. yes	0.34	0.13–0.92	0.04

Similar results were obtained when analysis was limited to patients with *in vivo* diagnosed IVL. IVL, intravascular lymphoma; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; RR, relative risk; CI, confidence interval.

of the patients with neurological symptoms and *in vivo* diagnosis of IVL. Conversely, in two cases, brain lesions were not associated with symptoms, but were detected during staging. Thus, in spite of possible false-negative results, MRI of the CNS should be routinely included in the current staging work-up of IVL. The presence of neoplastic cells in the cerebrospinal fluid (CSF) is rare, usually being present in an advanced phase of disease (Ossege *et al*, 2000), and in association with increased CSF protein levels, which is actually a more common finding (Wrotnowski *et al*, 1985; Nakahara *et al*, 1999; Vieren *et al*, 1999).

It has been commonly reported that haemolymphoid organs are usually spared in IVL; for example, bone marrow involvement has been rarely reported in IVL patients (Glass *et al*, 1993; Demirer *et al*, 1994). In our series, bone marrow involvement was observed in one-third of IVL patients, and was significantly associated with hepatosplenic involvement and pancytopenia. As in one of our cases, the bone marrow may remain the only detectable site of disease, allowing IVL diagnosis, for example, in patients with persistent unexplained fever. Taken together, these features suggest that a bone marrow biopsy should be performed in IVL patients, for both diagnostic and staging purposes. Our observations indicate that the involvement of haemolymphoid organs in IVL patients shows a peculiar pattern; conversely to what is observed in most non-Hodgkin's lymphoma (NHL) cases, lymph node involvement is rare (11% of our cases), while hepatic, splenic and marrow infiltration is present in one-third of cases.

As also confirmed by our findings, pulmonary IVL is characterized by multifocal disease leading to dyspnoea, air trapping and severe pulmonary hypertension, with a rapidly aggressive behaviour (Snyder *et al*, 1989; Ko *et al*, 1997; Jang *et al*, 1998; Walls *et al*, 1999; Evert *et al*, 2000; Owa *et al*, 2000). Endocrine gland involvement is common, with a variable presentation according to the infiltration of one or more organs (Chu *et al*, 1996; Hanihara *et al*, 1996; Shanks *et al*, 1997). Interestingly, IVL can be associated with solid tumours (Rubin *et al*, 1997; Shanks *et al*, 1997; Wang *et al*, 2001). In our series, one case was diagnosed within a renal cell carcinoma, while IVL cells were also detected within an hepatic haemangioma in two cases. The preferential involvement by IVL cells of solid tumour-associated vessels seems to suggest the presence of basic, unknown mechanism(s) involving adhesion molecules. In these cases, reactive or neoplastic endothelia may act as a selective attraction for neoplastic lymphocytes. Consequently, IVL may be a good candidate for the evaluation of lymphocytic migration, traffic and invasiveness of lymphoma cells (Ponzoni *et al*, 2000).

Some cases of IVL have arisen in patients with a previous history of NHL (Carter *et al*, 1996; Gabor *et al*, 1997). In most cases, IVL is concomitant or subsequent to a large B-cell lymphoma (Bhawan *et al*, 1985; Wick *et al*, 1986; Lopez-Gil *et al*, 1992; Glass *et al*, 1993), but cases of IVL developing after small lymphocytic lymphoma (Glass *et al*, 1993) or follicular

lymphoma (Carter *et al*, 1996) have also been reported. In two of our cases, IVL was diagnosed in patients previously affected by a gastric B-cell marginal zone lymphoma of MALT-type and a diffuse large B-cell lymphoma of the salivary gland. Evidence of a common clonal origin is lacking. However, this is a very relevant issue considering that extravascular infiltration, which was observed in 11% of our cases, does not exclude the diagnosis of IVL, since the co-existence of both components has been previously described (Ansell *et al*, 1982; Bhawan *et al*, 1985; Stroup *et al*, 1990; DiGiuseppe *et al*, 1994).

Among the laboratory findings, increased serum levels of LDH and  $\beta$ 2-microglobulin were present in almost 90% of cases, while anaemia was present in two thirds of cases. Altered hepatic (Gabor *et al*, 1997; Owa *et al*, 2000; Koizumi *et al*, 2001), renal or endocrine functional tests (Al-Chalabi & Abbott, 1995; Nakahara *et al*, 1999; Ramus & Booth, 1999) and increased CSF protein levels (Bhawan *et al*, 1985; Wrotnowski *et al*, 1985; Stroup *et al*, 1990) are common features in IVL, and, according to our findings, these function tests are useful tools in staging IVL; abnormal results were invariably associated with organ involvement by lymphoma cells.

The clinical features in our series are remarkably different to those reported in Japanese series (Murase & Nakamura, 1999; Takahashi *et al*, 1999; Shimazaki *et al*, 2000). In Japanese patients, IVL is associated with haemophagocytic syndrome, bone marrow involvement, fever, hepato-splenomegaly, and thrombocytopenia in 73–100% of cases, while CNS and cutaneous involvement are uncommon (Murase & Nakamura, 1999). Some Japanese authors claimed these features are diagnostic for IVL-associated haemophagocytic syndrome (named also 'Asian variant') (Shimazaki *et al*, 2000). In the Japanese series, IVL showed a rapidly aggressive behaviour, with a median survival of 2–8 months (Takahashi *et al*, 1999), which is in line with the previously reported negative prognostic impact of the haemophagocytic syndrome in haematological malignancies (Majluf-Cruz *et al*, 1998).

Data from the present series suggest that any patient with the diagnosis of IVL should be considered to have disseminated disease, and should be treated accordingly with intensive, combined chemotherapy; with a few exceptions, patients managed without this strategy died early. Only patients with a single, small cutaneous lesion, for who chemotherapy is contraindicated, could be managed with radiotherapy alone with some probability of cure. Anthracycline-based chemotherapy appears the best choice considering that the exclusion of these drugs has been associated with disappointing outcome (Stroup *et al*, 1990; Kuwabara, 1999; Evert *et al*, 2000). Fifty-eight percentage of our patients treated with CHOP (cyclophosphamide, adriamycin, oncovin, prednisone) or a CHOP-like regimen achieved an objective response, with a 3-year OS of  $32 \pm 11\%$ . In the English literature, many cases treated with this combination showed clinical benefit, but follow-up is usually short (DiGiuseppe *et al*, 1994; Baumann *et al*, 2000; Savarese *et al*, 2000). Since, the same strategy has been followed by inexorable progression in many other cases



(Ko *et al*, 1997; Rubin *et al*, 1997; Takamura *et al*, 1997; Vieren *et al*, 1999; Owa *et al*, 2000), some authorities suggested that chemotherapy benefit could actually reflect a selection bias.

Intensified therapeutic approaches could improve current outcome. High-dose chemotherapy supported by ASCT, an important strategy to intensify treatment against NHL, is however, feasible only in a small proportion of IVL patients considering that their median age is 70 years and PS is usually poor. Worldwide experience with this strategy in IVL is limited, with some encouraging results both as first- (Koizumi *et al*, 2001; Yamaguchi *et al*, 2001) and second-line treatment (Rose *et al*, 1999); however, it is possible that some unsuccessfully treated IVL patients have not been reported. In our series, four patients were treated with this strategy; two women treated with high-dose chemotherapy supported by ASCT as consolidation after MACOP-B or CHOEP were alive and relapse-free after 19 and 71 months; whereas the two patients treated with this strategy as salvage therapy for systemic relapses died early after transplantation, because of toxicity or progression.

The identification of clinical, histopathological and biological features that are useful for distinguishing different risk groups is a relevant issue in the therapeutic management of these rare lymphomas. In the present series, disease limited to the skin at presentation ('cutaneous variant'), ECOG-PS >1 and stage-I disease were independent favourable predictors of survival. Importantly, as suggested by limitations in standard lymphoma staging, a negative systemic staging not necessarily defines a stage-I disease. Negative staging may be consistent with the presence of a minor tumour burden in an usually disseminated disease, which could be associated with a better prognosis. Many patients with 'stage-I disease', good PS and 'cutaneous variant' obtained prolonged remission with conventional anthracycline-based chemotherapy. However, survival of IVL patients treated with this approach is disappointing, and more intensive strategies should be investigated in younger patients with unfavourable features.

Patients with IVL limited to the skin at presentation displayed distinctive clinical characteristics and prognostic profile. In fact, all patients with the 'cutaneous variant' were females and had normal leucocyte and platelet counts. Almost all patients with 'cutaneous variant' had an excellent PS, were younger and less frequently had B symptoms and bone marrow infiltration. Conversely, other laboratory findings-like elevated serum LDH levels, anaemia and an elevated ESR, were observed with the same frequency in patients with 'cutaneous variant'. From a prognostic standpoint, patients with 'cutaneous variant' of IVL survived significantly longer than the others, which was independent of the IPI and all other prognostic variables investigated. However, therapeutic outcome was remarkably different between patients with single and multiple cutaneous lesions. All cases with single cutaneous lesions were long-term survivors, while patients with multiple lesions showed worse outcome. In some cases with single lesions, local strategies were associated with a prolonged

remission, both at diagnosis and relapse. Cases with multiple cutaneous lesions were mainly treated with systemic anthracycline-based chemotherapy, with an objective response in 86% of cases. Nevertheless, the majority of these patients relapsed within a year of treatment, and only a few cases were successfully managed with salvage chemotherapy.

The favourable clinical behaviour of the 'cutaneous variant' of IVL, mainly in cases with a single lesion, may be simply explained by the easier and earlier diagnosis of cutaneous lesions or, alternatively, by potential biological and behavioural differences with respect to the rest of IVL cases; these still unanswered questions will be addressed in planned forthcoming studies.

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