

The Neurological Masquerade of Intravascular Lymphomatosis

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Background: Intravascular lymphomatosis (IVL) is an uncommon systemic disease characterized by occlusion of small vessels by malignant lymphomatous cells. Central nervous system involvement usually presents as subacute encephalopathy, dementia, seizures, or multifocal cerebrovascular events.

Objective: To increase awareness about IVL, an uncommon cause of neurological disease.

Design: This is a retrospective case series of 8 pathologically proved cases of IVL with neurological disease. Patients were part of a pathological series collected between April 1962 and October 1998 at Indiana University School of Medicine and the Armed Forces Institute of Pathology, Washington, DC.

Setting: Neurological and neuropathological examinations were performed at tertiary referral hospitals.

Patients: Eleven patients were diagnosed pathologically as having IVL, but 3 were not included in this eval-

uation because of a lack of appropriate clinical information. Of the final sample (n=8), there were 4 men and 4 women (mean±SD age, 62.9±9.9 years).

Results: All 8 patients had focal neurological deficits, 7 had encephalopathy or dementia, 5 had epileptic seizures, and 2 had myelopathy. Death occurred at a mean of 7.7 months (range, 1-24 months) after the onset of symptoms. All patients had elevated cerebrospinal fluid protein levels, 4 had pleocytosis, and 2 had an elevated IgG level in their cerebrospinal fluid. Of the 4 patients who underwent a brain biopsy, 1 was diagnosed as having IVL before death.

Conclusions: Intravascular lymphomatosis is an uncommon disease with a myriad of potential neurological manifestations. Diagnosis requires a high index of suspicion and a pathological examination. If diagnosed early, aggressive chemotherapy is potentially curative, although the overall prognosis remains dismal.

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INTRAVASCULAR lymphomatosis (IVL), also known as angiotropic large-cell lymphoma or malignant angioendotheliomatosis, is an uncommon systemic disease characterized by the occlusion of arterioles, capillaries, and venules throughout the body by malignant lymphomatous cells. The signs and symptoms of the disorder are attributed to vascular occlusion.^{1,2} Of the patients with IVL, 75% to 85% have central nervous system (CNS) involvement and more than 90% may develop multifocal cerebrovascular events, dementia, subacute encephalopathy, seizures, and myelopathy. Neuropathies, radiculopathies, and myopathies are also possible.³⁻⁵ Other organs may be involved, including the kidneys, the liver, the lungs, the prostate, skin, and the thyroid gland. However, hematopoietic organs are usually spared.^{4,5} Because of the lack of in-

volvement of the reticuloendothelial system, peripheral blood, or bone marrow by the lymphomatous process, diagnosis is often delayed or determined at autopsy.⁶⁻¹³ Spontaneous remission in untreated patients is possible,¹⁴ but the clinical course is usually fatal in a few weeks to several months.^{10,15,16} However, aggressive chemotherapy early in the disease process increases survival and is potentially curative.¹⁷

RESULTS

Intravascular lymphomatosis was fatal within a mean±SD of 7.7±7.6 months (range, 1-24 months) of the onset of symptoms. All patients developed focal neurological deficits, and multiple brain regions were affected. The most common focal deficits were motor and sensory deficits (n=6) and aphasia (n=5). Less fre-

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PATIENTS AND METHODS

This is a retrospective case series evaluation of 8 patients from a sample of 11 persons with pathologically proved IVL who were examined at Indiana University School of Medicine and the Armed Forces Institute of Pathology between April 1962 and October 1998.¹⁸ The 3 patients eliminated from this description did not have adequate clinical information available for review. They were men, aged 32, 47, and 76 years. The 32-year-old patient had a myelopathy and a brain lesion that, after biopsy, confirmed the diagnosis of IVL. Of the remaining 8 patients with IVL described in this series, 1 had a *Mycobacterium marinum* infection, and we described him previously.¹⁹ Of the 8 patients, 4 were men and 4 were women (mean \pm SD age, 62.9 \pm 9.9 years; range, 42-74 years). All of them were white. Details regarding demographic characteristics and clinical findings are shown in **Table 1**.

quently, dysarthria, apraxia, incoordination, cogwheel rigidity, and akinetic mutism were found. Four patients initially presented with mental status changes, and 3 developed them during the later stage of the disease. Mental status changes included confusional states with a fluctuating level of alertness and a decline in cognitive status with rapidly progressive dementia. Two patients had myelopathy with paraparesis and urinary incontinence. Of these 2 patients, 1 (patient 5) initially had an undifferentiated malignant lymphoma and underwent pelvic and lumbar spine radiation therapy plus cyclophosphamide administration, with improvement of symptoms for 8 months, when she developed sudden global aphasia, right hemiparesis, and generalized seizures. This patient died 1 year after the beginning of symptoms. Five patients had epileptic seizures. In 4 of them, the seizures were focal and tended to occur with more advanced disease. One patient with rapidly progressive dementia (patient 4) developed multifocal startle myoclonus and was thought to have Creutzfeldt-Jakob disease until a postmortem brain biopsy specimen demonstrated IVL. Another patient with focal neurological findings and progressive dementia (patient 6) was thought to have Creutzfeldt-Jakob disease when the brain biopsy specimen showed evidence of neuronal lipid degeneration and astrocytic gliosis. Weight loss, fever, and malaise were present in 5 patients. Two patients had skin manifestations: one had a maculopapular rash on the left hand, and the other presented with generalized eczema. The latter patient underwent a skin biopsy, and the biopsy specimen showed perivascular infiltration suggestive of a chronic inflammatory process.

All the patients had elevated protein levels in their cerebrospinal fluid (CSF). Four patients had mild pleocytosis, and only 1 had atypical cells. Two patients had high levels of lactate dehydrogenase, and 3 had anemia. One patient (patient 8) had elevated levels of anti-nuclear antibodies (1:5120) and phosphatidylethanolamine (IgM 8 multiples of the mean [normal values \leq 4

multiples of the mean]). This patient responded transiently to corticosteroids and was thought to have primary CNS angiitis until autopsy, when the diagnosis of IVL was confirmed. One patient had a history of Waldenström macroglobulinemia. This patient developed focal and diffuse neurological deficits, with no laboratory evidence of hyperviscosity syndrome.

Only 1 of 3 brain biopsy specimens obtained during life was diagnostic for IVL (in patient 3). Patient 3, at diagnosis, had a terminal prognosis and no chemotherapy was recommended; this patient died 2 months after the beginning of symptoms. The nondiagnostic biopsy specimens were not reevaluated, and both included samples of the leptomeninges. All the patients underwent an autopsy, except for a patient (patient 4) who underwent a postmortem brain needle biopsy for suspected Creutzfeldt-Jakob disease. Two patients had an autopsy that was limited to a brain evaluation. All patients had intraluminal lymphoma cell accumulation. Capillaries and veins were the vessels more commonly involved. Two patients had an extravascular extension of lymphoma cells, and one of them had a neoplastic perivascular infiltrate. Details regarding the pathological findings are shown in **Table 2**.

COMMENT

Most publications on IVL are either single case reports or short series. To our knowledge, this is the largest series of patients with neurological manifestations of IVL. According to the literature, the age of onset is in the sixth decade of life, with a male-female ratio between 1:1 and 2:1. Encephalopathy or cognitive decline is present in 85% of the patients, and focal symptoms are present in 67% to 82% of the patients.^{1,2,4,6-13,15,20,21} Seizures affect one fourth of the patients.^{10,12} Most frequently, seizures are generalized and occur late in the course of the disease.¹⁰ Myoclonus may affect patients with IVL, occasionally leading to the erroneous diagnosis of Creutzfeldt-Jakob disease.⁸ The clinical findings and demographic data in our patients are consistent with previous reports.^{1-5,9,10,21} Intravascular lymphomatosis may occur in patients with a history of follicular small cleaved cell lymphoma²⁰ and in patients with Waldenström macroglobulinemia,²¹ as was the case in 2 of our patients.

Dermatological manifestations are present in up to one third of the patients with IVL. These include nodules, indurated plaques, and telangiectasis.^{12,22,23} Constitutional symptoms, such as fever, weight loss, malaise, or asthenia, affect 25% to 50% of these patients.^{10,12} Death typically ensues between 5 and 11.4 months after disease onset, but may occur within a few days or as late as 33 months.^{2,5,6,10} Intravascular lymphomatosis is a known mimicker of primary angiitis of the CNS^{7,13,14}; this was the diagnosis of one of our patients until an autopsy was performed. This patient had elevated titers of anti-nuclear antibodies and antiphospholipid antibodies, conditions seen in patients with IVL and non-Hodgkin lymphoma.^{7,24}

There are 4 frequent laboratory abnormalities in patients with IVL: anemia, an elevated erythrocyte sedimentation rate, an elevated lactate dehydrogenase level,

Table 1. Demographic Characteristics, Neurological Symptoms, and Complementary Data in Patients With IVL*

Variable	Patient No.							
	1	2	3	4	5	6	7	8
Year of the evaluation	1994	1993	1994	1986	1978	1962	1964	1998
Age, y	64	73	74	66	59	42	63	62
Sex	M	F	F	M	F	M	M	F
PMHx	Mm	Wal	Breast ca	None	Lym	None	None	None
Working Dx	Mening	PML	Met	CJD	Lym	CJD	Myelopathy	Angiitis
Cognitive deficit	+	+	+	+	-	+	+	+
Myelopathy	-	-	-	-	+	-	+	-
Seizures	GTC	-	Focal	Myoclonus	Focal GTC	Focal	-	Focal
Treatment	Antibiotics	Corticosteroids	Symptomatic	None	Rad/cyclophosphamide	None	Laminectomy	Corticosteroids
Death, mo	8	1	2	3½	12	24	2	9
Levels of analytes in the CSF								
Protein, g/dL	0.099	0.193	0.074	0.086	0.260	0.062	0.081	0.047
Glucose, mg/dL†	48	70	62	53	60	50	74	56
WBC count (10 ³ /μL)	10	46	5	0	8	2	6	4
ESR, mm/h	1	NA	NA	NA	NA	NA	NA	47
LDH, IU/L	1748	241	NA	NA	NA	NA	NA	1200
Hematocrit, %	NL	26.0	32.2	NA	26.0	NA	NL	40.0
Head scan findings								
CT	NA	Infarct	Infarct	NL	ND	ND	ND	Infarct and Hrg
MRI	Infarct	Infarct	Hrg	ND	ND	ND	ND	Infarct and Hrg

*Focal neurological deficits were present in all patients. Breast ca indicates ductal carcinoma of the breast, treated surgically; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; CT, computed tomography; Dx, diagnosis; ESR, erythrocyte sedimentation rate; GTC, generalized tonic-clonic seizures; Hrg, hemorrhage; IVL, intravascular lymphomatosis; LDH, lactate dehydrogenase; Lym, undifferentiated lymphoma; Mening, chronic meningitis; Met, brain metastasis of breast carcinoma; Mm, *Mycobacterium marinum* infection; MRI, magnetic resonance imaging; NA, not available; ND, not done; NL, normal; PMHx, significant previous medical history; PML, progressive multifocal encephalopathy; Rad, radiation therapy; Wal, Waldenström macroglobulinemia; WBC, white blood cell; +, present; and -, absent.

†To convert to millimoles per liter, multiply by 0.05551.

Table 2. Pathological Findings*

Variable	Patient No.							
	1	2	3	4	5	6	7	8
Autopsy	+	+	+	NA	+	+	+	+
Brain biopsy	ND	-	+	+†	ND	-	ND	ND
Intravascular‡	Capillaries and veins	Capillaries and veins	Capillaries and veins	Capillaries and veins	Capillaries and veins	Arterioles and veins	Capillaries and veins	Capillaries and veins
Lymphoid infiltrate								
Perivascular	+	+§	-	+§	-	-	+§	+§
Extravascular	+	-	-	-	-	-	+	-
Meninges	+	+	+	NA	+	+	+	+
Thrombus	+	+	-	-	+	-	-	+
Cell line	B	B	B	LCA	NA	NA	NA	B
Brain	Infarct	Infarct	Infarct	NA	Infarct and hemorrhage	Infarct	Infarct	Infarct and hemorrhage
PNS	ND	ND	ND	NA	Roots affected	NA	ND	NA
Lung	-	+	+	NA	-	NA	+	NA
Hematopoietic organs	-	+	+	NA	+	NA	-	NA
GU tract	+	+	+	NA	+	NA	+	NA
GI tract	+	+	+	NA	+	NA	-	NA
Cardiac	+	+	+	NA	+	NA	-	NA
Skin	-	ND	+	NA	ND	NA	ND	NA
Adrenal gland	+	+	-	NA	-	NA	-	NA

*+ indicates that a pathological finding was present; ND, not done; -, a pathological finding was absent; intravascular, intravascular, noncohesive malignant lymphomatous cells present; LCA, lymphocyte common antigen; PNS, peripheral nervous system; GU, genitourinary; GI, gastrointestinal; and NA, data not available.

†Post mortem.

‡The location of the finding is given.

§Reactive.

and an elevated CSF protein concentration. According to the literature,^{1-3,5-13,15} 45% of patients develop anemia, 75% have an elevated erythrocyte sedimentation rate,

85% have a lactate dehydrogenase level above 250 U/L, and 90% have an elevated CSF protein concentration. More than half of the patients have pleocytosis, and 3%

have atypical cells in the CSF. IgG elevation in the CSF is also possible.^{1,3,5-13,15} These findings were present in our patients.

A common observation is the occasionally dramatic but transient response to corticosteroid treatment.^{9,10,12,15} Different chemotherapeutic regimens have been attempted in patients with IVL,¹⁵ including M-BACOD (methotrexate, bleomycin sulfate, doxorubicin hydrochloride [Adriamycin], cyclophosphamide, vincristine sulfate, and dexamethasone), CHOP (cyclophosphamide, doxorubicin [Adriamycin], vincristine, and prednisone), COPP (cyclophosphamide, vincristine, procarbazine hydrochloride, and prednisone), and BACOP (bleomycin, doxorubicin [Adriamycin], cyclophosphamide, vincristine, and prednisone). There is evidence¹⁷ that aggressive chemotherapy after early diagnosis may induce remission and is potentially curative. However, the overall prognosis of patients with IVL remains dismal.

Most of the cases reported in the literature^{1,2,10,11,13,25} are postmortem evaluations or are diagnosed after a biopsy. Malignant lymphocytes usually show B-cell lineage,¹² and T-lymphocyte IVL is rare.²⁵ The characteristic microscopic findings are distention and occlusion of small cerebral and meningeal blood vessels by neoplastic mononuclear cells. Usually these cells are noncohesive and free in the lumina. Blood vessels may also show parietal infiltration by malignant cells, especially in subendothelial areas. However, most of the time this infiltration is caused by mature T lymphocytes.^{1,2,11,12} Only in rare instances do malignant cells extend beyond the vessel walls into the adjacent parenchyma.^{12,26} The neoplastic cells within the vascular lumina are frequently associated with thrombosis, resulting in ischemic infarcts of neural tissue.¹⁰ Vessel involvement is best seen adjacent to areas of infarction and necrosis.⁴ Brain infarcts or hemorrhages are common in patients with IVL. On the other hand, hematopoietic organ involvement is an uncommon feature, and only one of our patients had involvement of the spleen. Other organs that may be affected by IVL are the lungs, the kidneys, the prostate, the liver, the gastrointestinal tract, the thyroid gland, the heart, the adrenal glands, skin, muscle, and the peripheral nerves.^{1,2,4-13,15,20,25}

A condition that mimics IVL is lymphomatoid granulomatosis. This is a perivascular infiltrative lymphoma that, unlike IVL, is of T-lymphocyte lineage. Both conditions may involve the CNS and produce symptoms of dementia, multifocal infarcts, and seizures. Unlike the periventricular and white matter lesions seen in patients with IVL, lymphomatoid granulomatosis tends to involve the small vessels of the leptomeninges and the cortical blood vessels, causing diffuse cerebral atrophy without white matter changes on a magnetic resonance imaging scan.²⁷

The reasons for the intravascular localization of the neoplastic cells and their predilection to involve the CNS are not completely understood. It is known that endothelial cells can express surface receptors that facilitate lymphocyte attachment. Lymphocytes also have surface receptors for endothelial cells. An alteration in the normal interaction of endothelial cells and lymphocyte homing surface receptors on the neoplastic cells may be responsible for the intravascular location of the tumor. In addition, vessels of different organs might have organ-specific receptors.^{1,3,28}

The reason for the vascular occlusion in patients with IVL remains unclear. Most reports comment on the accumulation of atypical cells as the cause of the vascular occlusion. The origin of this intravascular accumulation is probably multifactorial. For instance, patients with IVL may present with hemolytic anemia, thrombotic microangiopathy, and disseminated intravascular coagulation. Thrombotic microangiopathy could have started after endothelial damage, leading to platelet activation, thrombocytopenia, red cell fragmentation, and microthrombi formation.⁶ Although this could be a reasonable explanation, none of our patients had clear evidence of disseminated intravascular coagulation, and we have not found any evidence supporting an important role for disseminated intravascular coagulation as a cause of vascular occlusion in patients with IVL. In the case of thrombotic microangiopathy, endothelial injury might be caused either by tumor-derived factors or by direct interaction of tumor cells with endothelial cells.⁶

Elevated antiphospholipid antibodies, including anticardiolipin antibodies and the lupuslike anticoagulant, may be seen in two thirds of patients with acute myelogenous leukemia and in almost half of patients with non-Hodgkin lymphoma, respectively.²⁴ This was the case in one of our patients who had an elevation of the phosphatidylethanolamine level. This could explain the tendency toward a prothrombotic state and partially account for the vascular occlusion in these patients.

In summary, IVL is a rare systemic disease that causes a myriad of neurological symptoms, including focal neurological deficits, cognitive decline, and seizures. Diagnosing IVL is challenging because the signs and symptoms are nonspecific and there is no diagnostic test other than a pathological examination. This lack of reliable ancillary tests delays the diagnosis and limits the efficacy of potentially curative chemotherapy. For this reason, the examination of these patients requires a high index of suspicion and an aggressive workup. This should include computed tomography or magnetic resonance imaging of the thorax, abdomen, and pelvis to examine organs usually involved in persons with IVL; a biopsy of the affected skin or viscera, and recommend brain with meningeal biopsy for those cases in which there is no other more accessible source of affected tissue. In cases in which a brain biopsy is to be performed, it is of utmost importance to include leptomeninges in the biopsy material (ideally, a cubic centimeter of cerebral cortex, subcortical white matter, and leptomeninges). In patients with IVL, the tissue fixed with formaldehyde solution is the most informative, because it is used for phenotyping of the malignant cells by immunohistochemistry.

The physiopathological features of this disorder are thought to be related to vascular occlusion, although the precise mechanisms of vascular-cellular interaction leading to vascular occlusion and thrombotic events are not clear. Further research to elucidate the mechanisms of vascular occlusion and identification of the factors that predispose to CNS involvement will be required to help develop more effective treatments for IVL.

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