

Cerebral MR Imaging in Intravascular Lymphomatosis

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Summary: MR imaging data were reviewed retrospectively in four male patients (32 to 74 years old) with histologically confirmed intravascular lymphomatosis (IVL), a rare, aggressive form of non-Hodgkin lymphoma. MR findings included infarct-like lesions (n = 2), focal parenchymal enhancement (n = 3), dural/arachnoid enhancement (n = 2), and, in one case, nonspecific, patchy foci of increased signal in the white matter on long-TR images. All patients had multifocal lesions. Knowledge of the spectrum of MR imaging features in this unusual disorder may aid in diagnosis and potentially enhance the role of imaging in following response to therapy.

Intravascular lymphomatosis (IVL) is a rare systemic disease with a predilection for the CNS and skin (1-3). This entity represents a form of large-cell non-Hodgkin lymphoma that is characterized by angiotropic growth (3). IVL was originally described by Pflieger and Tappeiner (4) in 1959 and designated angioendotheliomatosis proliferans systemisata. Since then, it has variously been referred to as neoplastic angioendotheliosis, malignant angioendotheliomatosis, and angiotropic large-cell lymphoma (3, 5-7). Initial confusion over the appropriate term for this disease stemmed from its unclear histogenesis. However, it is now well accepted that IVL represents a malignant lymphoma, most commonly of B-cell lineage.

Pathologic diagnosis of IVL may be difficult and requires immunologic analysis and electron microscopy. Light microscopy will reveal a neoplastic proliferation of large, pleomorphic mononuclear cells with prominent nucleoli typically found within the lumina of capillaries, venules, arterioles, and small arteries. IVL predominantly affects vessels in the skin and CNS but may involve any organ (2, 7). Unlike leukemia, IVL is not characterized by malignant cells in the peripheral blood smear or bone marrow replacement (3).

The clinical presentation of IVL is frequently nonspecific and may consist of changes in mental status, nonlocalizing neurologic deficits, seizures, fever of unknown origin, or skin changes (6). When combined with the only common laboratory finding of a mild to moderate elevation of CSF protein, it is not surprising that the diagnosis may be delayed. The advanced stage at presentation may also contribute to the overall mortality rate of greater than 80% and an average survival time of only 9 to 13 months (2, 8-10).

The diagnostic imaging of IVL has been equally nonspecific, contributing to the difficulty of achieving an antemortem diagnosis (8). Angiography and computed tomography (CT) often show evidence of multiple vascular occlusions and stroke (10). A few individual case reports of IVL have included cerebral magnetic resonance (MR) imaging findings, with various appearances reported (1, 8, 10-14). We collected four cases of IVL in which MR images showed brain involvement. Our aim was to characterize the MR appearance of this entity through review of our imaging data and that in the literature.

Methods

We collected and retrospectively reviewed four cases of IVL from our case records and archives of the Armed Forces Institute of Pathology. All the patients in our series were male, none immunocompromised. Ages ranged from 32 to 74 years, with a mean age of 59 years. Three patients presented with altered mental status and one patient had seizures. Histology was confirmed in all cases; stereotactic brain biopsies were performed in cases 1 and 2, an operative lung biopsy and a needle biopsy of the liver were performed in case 3, and a craniotomy with brain biopsy was performed in case 4.

All tissues were fixed in 10% neutral formalin and embedded in paraffin. Five-micrometer sections were stained with hematoxylin-eosin or according to the avidin-biotin-peroxidase complex procedure as described previously (15) using antibodies to CD20 (Dako Corp, Santa Barbara, Calif), a cytoplasmic antigen in B-lymphocytes; CD3 (Dako Corp), a marker for

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Summary of MR findings in patients with intravascular lymphomatosis

Case	Age/ Sex	Clinical Signs/ Symptoms	MR Findings				Contrast Administration	Enhancement		Multifocal Lesions
			Normal	Nonspecific White Matter Changes	Infarctlike	Focal Mass Lesion		Meningeal	Parenchymal	
1	74/M	Altered mental status	...	Patchy, diffuse	Y	Extensive dural/ arachnoid enhancement	...	Y
2	32/M	Weakness/confusion	R frontal, L parietal with extension to splenium	Y	...	L parietal, R frontal enhancement	Y
3	66/M	Confusion	R basal ganglia, L thalamus	L parietooccipital	Y	Dural/arachnoid and pial enhancement	Multiple foci of enhancement	Y
4	64/M	Seizures	L frontal and R parietal regions	R temporal	Y	...	Ring enhancement R temporal subcortical white matter	Y
Otrakji et al, 1988 (11)	68/M	Incontinence, severe paresis in L lower extremity	...	R > L hemisphere	N	Y
Fredericks et al, 1991 (10)	49/M	Progressive lethargy, confusion, dysphagia	...	Periventricular and deep white matter	L occipital, R frontal regions	...	Y	Extensive dural enhancement	L occipital lobe enhancement	Y
Glass et al, 1993 (1) (Patient 2)	62/M	Lethargy, confusion, fever	...	Multiple areas of abnormal increased signal in white matter	N	Y
Liszka et al, 1994 (8) (Case 3)	50/F	Generalized seizures, aphasia	Initial MR normal	L frontal and parietooccipital regions	N	Y
Daniel et al, 1987 (12)	59/M	Dysphagia, seizure	Small area of increased signal in L temporal cortex	...	N	N
Harris et al, 1994 (13)	43/F	Leg weakness, bowel and bladder symptoms	No enhancement on serial MR	Y	N.A.
Raroque et al, 1990 (14)	60/M	Seizures and paraparesis	Bilateral frontal lobes	Y	Questionable	Cortical enhancement, bilateral temporal, parietal, and occipital lobes	Y

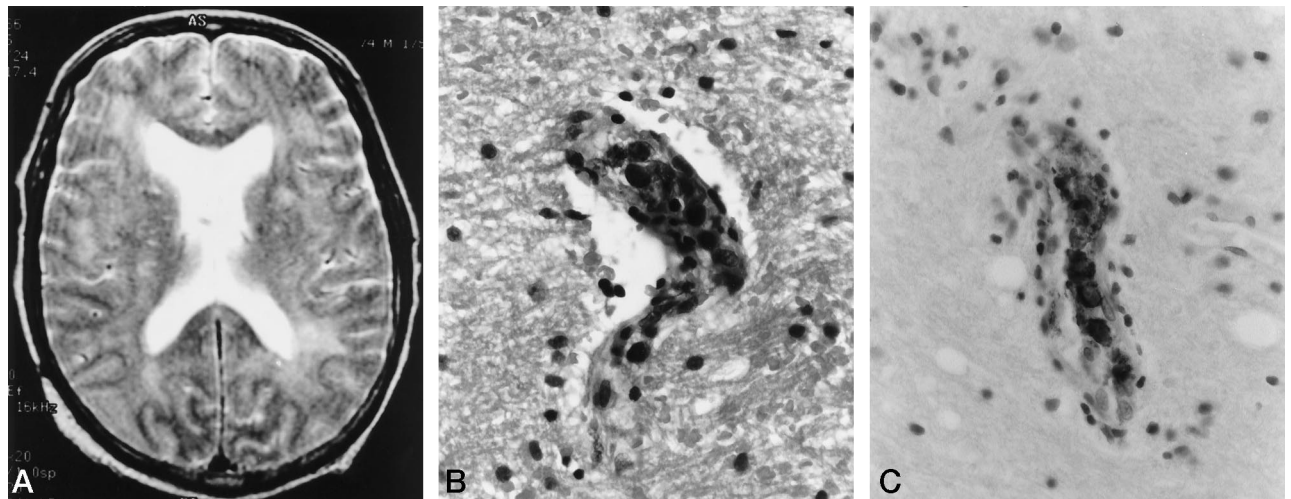


FIG 1. Case 1.

A, Axial T2-weighted MR image (2500/95/1) at the level of the body of the lateral ventricles shows diffuse patchy areas of white matter hyperintensity without mass effect.

B, Brain biopsy specimen shows atypical lymphocytoid cells within the lumens of the blood vessels (hematoxylin-eosin, original magnification $\times 400$).

C, Brain biopsy specimen stained for CD20 to show that the atypical cells are B-cell lymphocytes and are primarily found within the lumens of blood vessels (original magnification $\times 400$).

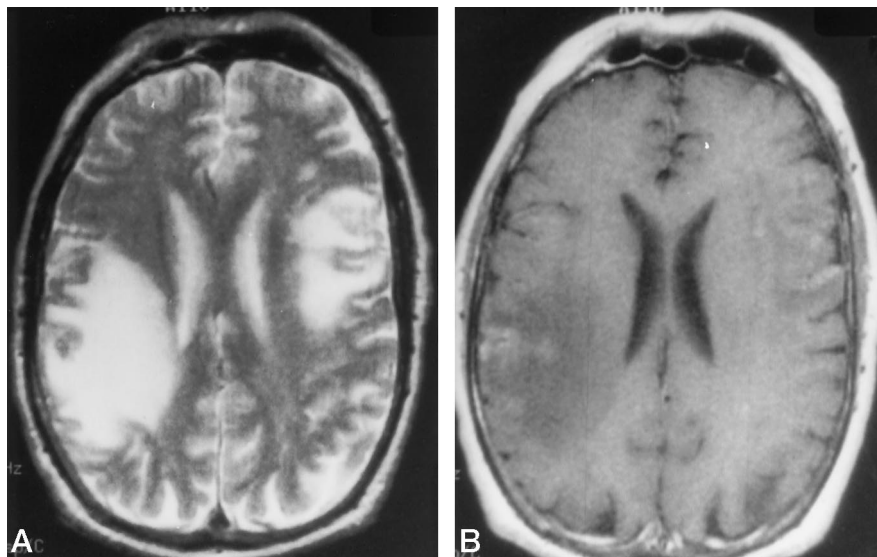


FIG 2. Case 4.

A, T2-weighted MR image (specific parameters are not available) shows two large areas of focal hyperintensity in the left frontal lobe and right parietal region.

B, Contrast-enhanced T1-weighted image shows corresponding gyriform enhancement, consistent with infarction.

T-lymphocytes; and von Willebrand factor (Dako Corp), a marker for the endothelial cells of blood vessels.

MR imaging data were collected from various institutions, in which diagnostic MR imaging was performed an average of 5.5 weeks (range, 1 to 14 weeks) after initial presentation. All institutions used standard clinical pulse sequence techniques at 1.0 or 1.5 T. The MR examinations evaluated were the initial study in all except case 3. In this instance, the first two studies were nondiagnostic owing to severe motion artifacts, accounting for the prolonged interval of 14 weeks from clinical presentation to diagnostic imaging. T1-weighted (400–783/15–31 [TR/TE]) and fast spin-echo T2-weighted (2500–4000/80–108 [TR/TE_{eff}]) images were available for all patients. Each patient also had MR imaging after intravenous administration of 0.1 mmol/kg of gadoteridol or gadopentetate dimeglumine.

The images were evaluated by three neuroradiologists for signal-intensity abnormalities and enhancement characteristics. Imaging findings were categorized as normal, nonspecific white matter changes (increased signal intensity on long-TR images without mass effect or enhancement); infarctlike; or suggestive

of a mass lesion. The criteria used for the infarctlike category included involvement of gray matter, increased signal intensity on long-TR pulse sequences, involvement of a vascular territory, and presence of minimal or no edema. The criteria used to define a mass lesion included increased signal on long-TR images, extensive surrounding vasogenic edema and mass effect, and presence of nodular enhancement.

To complement the MR imaging data from our four cases, seven individual case reports of IVL with MR imaging were also reviewed (see Table). The MR data from the case reports were grouped into the same categories as described above on the basis of either the authors' description or our consensus review of the images.

Results

MR imaging of the brain showed multifocal abnormalities in all four cases (see Table). The most common abnormality was a mass lesion in three cases. Infarctlike findings were present in two cases, and nonspecific white matter changes were found in

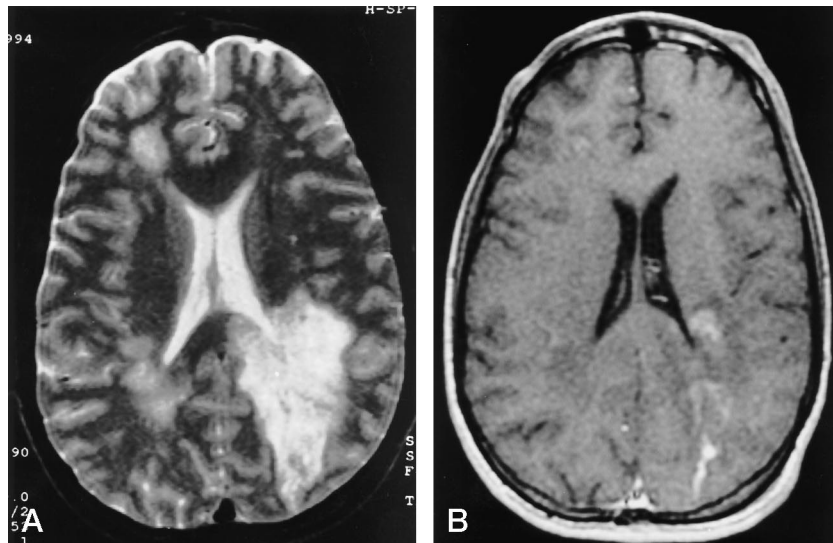


FIG 3. Case 2.

A, T2-weighted MR image (4000/80/1) shows gross hyperintensity in the left parietooccipital white matter with extension into the splenium of the corpus callosum. Additional smaller foci of hyperintensity are present in the right frontal and right parietal deep white matter.

B, Corresponding contrast-enhanced T1-weighted MR image (4000/15/2) shows multiple discontinuous foci of nodular enhancement within the left parietal lobe and splenium, suggestive of a mass lesion.

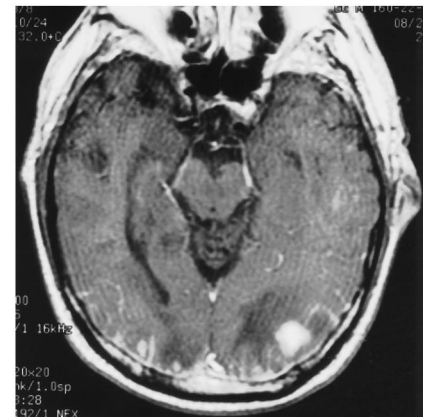


FIG 4. Case 3. Contrast-enhanced T1-weighted MR image (500/26/1) shows a focal enhancing lesion in the left occipital lobe and prominent bioccipital dura/arachnoid and pial meningeal enhancement.

only one case. In two cases, more than one pattern was exhibited. Enhancement was observed in all four cases. In two cases, meningeal enhancement was present. Parenchymal enhancement was seen in three cases: multifocal and nodular in two cases and ringlike in one case.

Microscopic examination revealed intravascular lymphoma in all cases. The neoplastic cells had irregular nuclei, coarse chromatin, and scant cytoplasm. At immunohistochemical staining, the neoplastic cells stained positively for leukocyte common antigen. Stains for endothelial cells, such as Ulex European lectin and factor VIII antigen, highlighted the blood vessels but did not stain the neoplastic cells. Three of the four cases expressed B-cell markers, while one case was of a T-cell phenotype.

Discussion

Intravascular lymphomatosis is a rare form of non-Hodgkin lymphoma; in one large series of patients with non-Hodgkin lymphoma of the CNS, IVL accounted for only two of 104 cases (16). Although this entity is well recognized in the literature, its MR imaging appearance has not been characterized in detail. This neoplasm exhibits striking angiotropic growth that leads to various clinical presentations, depending on the location of the vascular occlusions (1, 7).

The diffuse nature of brain involvement in this disease is reflected in its MR appearance. All patients in our series had multifocal abnormalities, a finding that is supported by the literature review, in which five of seven reports indicated multifocal disease (1, 8, 10, 11, 14). Furthermore, in a postmortem study of five cases of IVL, Clark et al (7) reported widespread evidence of atypical cells filling the lumina and involving blood vessel walls in the subarachnoid space, cortex, deep gray matter structures, and white matter.

In combining our results with the findings reported in the literature ($n = 11$ cases), the single most common imaging finding of abnormal, increased signal intensity on long-TR pulse sequences in the deep white matter (five of 11 cases, 45%) appears to correlate with edema and gliosis as seen in the biopsy specimen of case 1 (Fig 1). Some investigators speculate that small-vessel occlusion leading to ischemia and infarction is responsible for this imaging finding (11), which, in the absence of clinical information, may be nonspecific and difficult to distinguish from age-related white matter hyperintensity (17).

Infarctlike lesions were present in four (36%) of 11 cases (Fig 2), correlating with the most commonly reported pathologic finding of multiple areas of recent or resolving infarction (5, 7). The absence of definite signs of infarction on MR images in the remaining cases is surprising given that widespread vascular occlusion is often observed pathologically. This discrepancy may in part be the result of the nonspecific nature of abnormal, increased signal intensity on long-TR images in the deep white matter. Furthermore, the angiotropic growth of this neoplasm mainly affects small vessels and would not be expected to produce "classic" gray-white matter infarctions. The white matter hyperintensity and infarctlike lesions may subsequently represent a continuum of ischemic changes reflecting vascular occlusions in IVL.

Enhancing parenchymal mass lesions, mimicking other forms of lymphoma, were observed in three of the four cases in our series, but were only noted in one case in the literature. Additionally, focal nodular enhancement extending into the splenium of the corpus callosum was noted in case 2 (Fig 3). Although,

classically, IVL is thought to remain strictly confined to vascular lumina in the neural parenchyma (3), callosal involvement may represent extravascular spread of tumor. This point is supported in a report by Glass et al (1) in which similar imaging features on CT correlated with the postmortem histopathologic finding of both intravascular and extravascular foci of IVL in the corpus callosum. Although extravascular extension was not shown in case 2, tumor sampling was limited in this stereotactic biopsy specimen.

Extensive meningeal enhancement was present in two of our cases and in one previous case report (Fig 4). The pathogenesis of this finding may be multifactorial. Direct infiltration of meningeal blood vessels with IVL has been documented in several studies (3, 5, 10, 12, 18). Specifically, microinfarcts of the meninges or sluggish flow through their vessels may contribute to this finding. Subarachnoid seeding by tumor is not, however, considered a likely cause, since it is rarely found at autopsy (5).

Other diagnostic considerations in the setting of multifocal brain lesions with accompanying rapidly progressive dementia include cerebrovascular disease, infection, and neoplasia. Multiple cerebral emboli may result in multiinfarct dementia; however, the clinical history usually discloses abrupt episodes of neurologic deterioration as opposed to the more insidious neurologic compromise of IVL (7). Vasculitis may be considered a cause of small-vessel occlusions with resulting gray or white matter abnormalities on MR imaging. However, the extensive dural/arachnoid enhancement found in some cases of IVL would be atypical for vasculitis. The absence of rapidly progressive atrophy may distinguish IVL from Creutzfeldt-Jakob disease. Other infectious causes, such as progressive multifocal leukoencephalopathy, may be considered; however, the lack of host immune compromise makes this entity unlikely. Herpes encephalitis also may usually be excluded on the basis of the lack of appropriate findings in CSF studies and imaging that classically shows a predilection for the limbic system. Gliomatosis cerebri may mimic IVL clinically, but this entity tends to diffusely infiltrate white matter pathways, producing extensive hyperintensity on long-TR sequences and mass effect; the findings of contrast-enhanced foci and meningeal enhancement would also be unusual for this disease (19).

Conclusion

While IVL is rare, this diagnosis should be considered in patients presenting with nonfocal neurologic deficits or rapidly progressive dementia without documented cerebrovascular disease or immunosuppression. The MR findings arise in part from vessels occluded by IVL, producing a wide spectrum of abnormalities that are characteristically multifocal. These lesions may range from nonspecific white matter changes to infarctlike lesions. The MR appear-

ance of IVL may also manifest as enhancing mass lesions, possibly predicting extraluminal spread of disease. Recognition of the MR findings in IVL may lead to prompt biopsy, allowing earlier diagnosis and treatment, and potentially affecting patient survival.

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