

Intravascular Lymphoma Masquerading as Multiembolic Stroke Developing After Coronary Artery By-Pass Surgery

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Background: Intravascular lymphoma (IVL) is a very rare non-Hodgkin type lymphoproliferative disorder characterized by neoplastic growth of lymphoid cells within the lumen of capillaries, small veins, and arterioles. The neoplastic cells cannot reach the parenchyma because of the loss of adhesion molecules during malignant transformation. Multifocal vascular occlusions caused by proliferation of malignant lymphocytes in the lumen result in diffuse thrombosis and tissue infarction. The clinical symptoms of the disease are dependent on the specific organ involvement which most often includes the central nervous system and skin. Neurologic presentation includes focal sensory or motor deficits, altered sensorium, rapidly progressive dementia, seizures, ataxia, and vertigo.

Case Report: We report a patient with IVL whose symptoms developed on the second postoperative day of coronary artery-bypass surgery imitating a multiembolic stroke. Magnetic resonance imaging showed widespread ischemic subcortical lesions. The patient's clinical status worsened irrespective of supportive medical treatment. The diagnosis was established by autopsy.

Conclusion: IVL may mimic ischemic stroke. IVL is not often diagnosed before death because of the intravascular growth pattern of the tumor cells and a fulminant clinical course. IVL may be considered in the differential diagnosis of ischemic stroke patients with progressive worsening despite medical management.

Key Words: intravascular lymphoma, central nervous system

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Intravascular lymphoma (IVL) is a non-Hodgkin lymphoma, in which the malignant lymphocyte clone is restricted to the lumen of small and medium sized blood vessels. Vascular occlusion results in tissue infarction. IVL is an extremely rare and aggressive disease. It predominantly affects elderly patients. Despite the fact that all organs may be affected, the most commonly involved organs are the central nervous system (CNS) and skin.^{1,2} Patients usually present with progressive encephalopathy with focal neurologic deficits and skin petechiae, purpura, plaques, and discoloration. The diagnosis is seldom made during life because of the rarity of the disease, its potential of mimicking a broad spectrum of diseases and lack of specific diagnostic tools except for pathologic examination. Nearly half of the cases are diagnosed only after autopsy and many of the antemortem diagnoses are made incidentally in biopsies performed for different purposes.^{3,4} The literature on IVL is almost exclusively limited to case reports and cumulative reviews. Here we report a patient whose clinical signs developed following coronary artery—bypass surgery imitating multiembolic ischemic stroke.

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CASE REPORT

A 54-year-old man who had stable angina pectoris had coronary artery-bypass surgery in August 2006. There were no perioperative or postoperative complications reported. After surgery, the patient regained consciousness, spoke understandably and was appropriate. He could walk and eat without assistance. There was no abnormality noted until the second day following surgery when he began speaking nonsense. Visual hallucinations occurred and he could not sleep. Brain computerized tomography was normal. Meanwhile his blood urea nitrogen and creatinine levels increased and he was diagnosed with renal insufficiency. Intravenous fluids were added and his metabolic condition returned to normal within a week. However his mental status worsened. Aggressive behavior, decreased oral intake, and difficulty in walking increased daily.

In the second week following surgery, magnetic resonance imaging (MRI) showed multiple subcortical lesions in the cerebral and cerebellar hemispheres (Fig. 1A). Multiple embolic infarcts due to a shower of emboli soon after the bypass surgery was the initial diagnosis. He was discharged from hospital on acetylsalicylic acid 300 mg/d. His condition worsened further at home. He could barely speak and had incomprehensible words. He could not walk without assistance. Upon deterioration of his health, he was admitted to our hospital.

His general examination was unremarkable except for a right lower lobe pneumonia, which was considered a complication of aspiration. He did not cooperate with verbal stimuli. Aggressive bursts mixed with somnolence was present. He spoke with incomprehensible words. Motor examination revealed a 4 of 5 left hemiparesis and a right extensor plantar response. He was incontinent.

There was no history of hypertension, diabetes mellitus, or hypercholesterolemia. He was an ex-smoker; consuming 10 to 15 cigarettes a day for 30 years and had quit smoking 2 years previously. He was in his usual state of health until the bypass surgery.

Laboratory findings revealed a leukocytosis (12.400/mm³), an increased blood urea nitrogen (41.7 mmol/L; range 7.5–14) and creatinine (314.7 μmol/L; range: 80–115), lactate dehydrogenase (772; range:180–480 U/L) levels, and an increased erythrocyte sedimentation rate (107 mm/h). Antinuclear antigen, antidouble stranded DNA, and HIV serology were negative and blood cultures were sterile. There were no malignant cells in the peripheral blood smear. Other biochemical tests were unremarkable.

Cranial MRI was repeated on the day after admission and the 33rd day of his symptoms. New subcortical hyperintense

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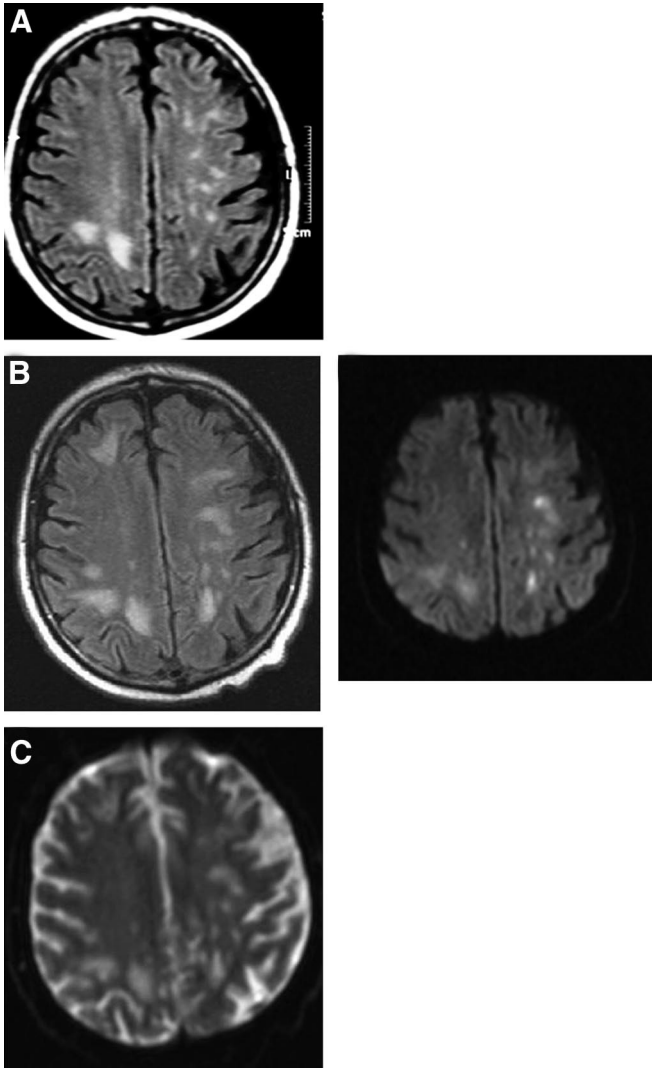


FIGURE 1. A, MRI FLAIR sequence on the 14th day of patient's symptoms. Multiple, subcortical hyperintense lesions are present in both parietal lobes. B, FLAIR and $b = 1000$ DWI sequences shows multiple hyperintense lesions in both hemispheres. There is enlargement of the previous lesions and new lesion in the right frontal lobe when compared with A. C, The new lesions showed restricted diffusion in ADC maps.

lesions and the expansion of the old lesions were detected. New lesions had restricted diffusion whereas old ones had increased diffusion or pseudonormalization. Gadolinium enhancement was absent. Transesophageal echocardiography of the ascending aorta and duplex carotid ultrasonography showed no source of emboli. A 4-vessel digital cerebral angiography was performed to investigate the possibility of vasculitis and revealed no irregularities or aneurysmal dilatations. Electroencephalography revealed diffuse slowing. Lumbar puncture was performed and analysis of the cerebrospinal fluid was normal; the fluid was sterile and there was no malignant cells in the centrifuged sample.

A brain biopsy was proposed but was rejected by his relatives. 1000 mg/d of intravenous methyl-prednisolone was administered for the likely diagnoses of primary CNS vasculitis or IVL. The clinical

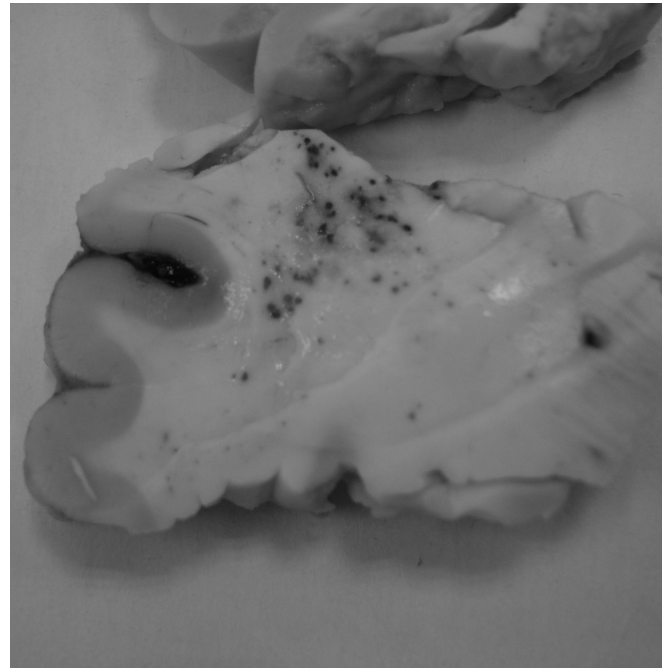


FIGURE 2. Hemorrhagic lesions from right frontal lobectomy (this area corresponded to the right frontal hyperintensity on Fig. 1B).

findings did not change during the first week of this treatment. He was still in a somnolent and agitated state and he responded by opening his eyes, hitting his surroundings with aimless sways, and grumbling to annoying stimuli. Cyclophosphamide (750 mg) single IV dose was added to the treatment regimen. The patient deteriorated and became comatose at the second day following the initiation of cyclophosphamide. Another MRI revealed expansion of the old lesions together with the presence of new ones (Figs. 1B, C). Respiratory failure developed the next day and mechanical ventilation was begun. On the 45th day following coronary artery bypass surgery, cardiac arrest developed and did not respond to cardiopulmonary resuscitation.

Postmortem frontal lobectomy was performed with the permission of his relatives and revealed multiple petechial hemorrhagic lesions (Fig. 2). Microscopic examination showed many of the blood vessels to be filled with large malignant lymphocytes. The cells had large nuclei and prominent nucleoli (Fig. 3). These malignant lymphocytes plugged the vessels and generally did not infiltrate the brain parenchyma. A more detailed examination with immunohistochemistry revealed B cell lymphoid cells that expressed leukocyte common antigen and CD20, but not CD3. Staining for immunoglobulin light chains disclosed that the neoplastic cells were monoclonal for intracytoplasmic lambda light chains while κ was negative. Thus, the definitive diagnosis of IVL of a B-cell subtype was established.

DISCUSSION

IVL is a systemic illness characterized by the proliferation of neoplastic lymphocytes within the lumen of small arteries, arterioles, capillaries and venules. IVL is typically a diffuse large B-cell lymphoma in which the tumor cells pack the lumen of small vessels without infiltrating the parenchymal tissue. It has a T-cell origin in 9% of IVL cases. Vascular occlusion results in tissue infarction. It is very rare, with an estimated frequency of <1% among all lymphomas. In contrast to other hematological malignancies, involvement of lymph nodes is usually absent. During the malignant transformation to

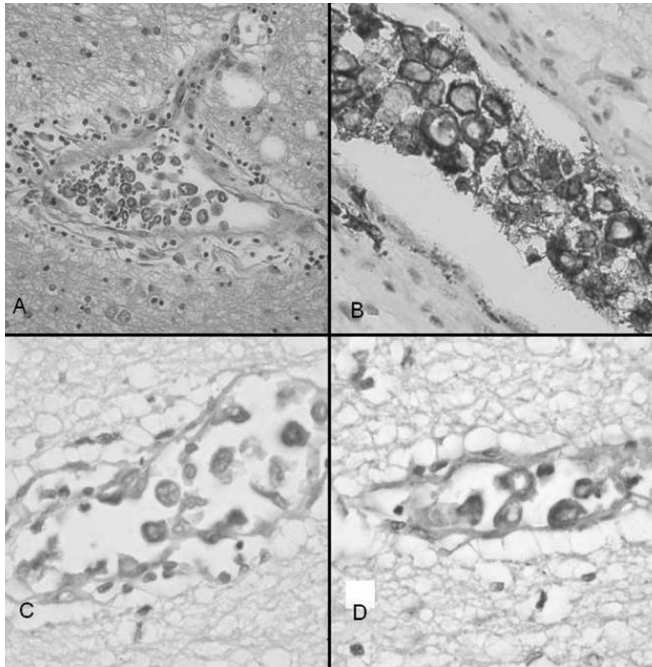


FIGURE 3. Section from the frontal cortex showing numerous large atypical lymphocytes within the lumen of a blood vessel. Note the irregular nuclei and multiple prominent nucleoli of the malignant cells. Hematoxylin and eosin, $\times 400$ (A). ABC peroxidase staining shows that the neoplastic cells are CD20⁺, $\times 1000$ (B). The cells contain intracytoplasmic lambda light chains, $\times 1000$ (C). They are negative for κ light chains, $\times 1000$ (D).

lymphoma, loss of expression of the homing receptors which are critical for crossing through the vascular walls and penetration to the parenchyma underlies the causative mechanism of this malignancy.⁵ Usually there are no circulating lymphoma cells in the blood or in the cerebrospinal fluid.^{1,3,4,6} Although the microangiopathy associated with IVL may involve any organ system, blood vessels of the CNS, and skin are most commonly affected. Infiltration of the lungs, kidneys, adrenal glands, or the prostate is also frequent. Liver, spleen, and bone marrow are relatively spared until the late stages of the disease.

IVL is extremely heterogeneous in its clinical presentation because of widespread presence of neoplastic cells in small vessels of nearly every organ. IVL is an aggressive and disseminated malignancy that affects patients mainly in the fifth decade of life or later. There is no gender prevalence.³ IVL is most common among transplantation associated or HIV related immunosuppressed patients.^{7,8} IVL was found to be associated with previous or concomitant neoplasia in 16% of patients.³ This may be associated with cancer related immunosuppression.

Classic presentation of IVL consists of CNS involvement, cutaneous involvement and fever of unknown origin.^{1,3,4,9,10} Domizio et al⁴ found CNS presentation in 56% of 78 patients based on their review of literature. Cutaneous involvement occurred in 56% and fever in 29% of the reviewed patients. In a multicenter clinical study, neurologic presentation was reported 34% of patients. This study was based on 38 patients who were diagnosed in 22 centers affiliated with the International Extranodal Lymphoma Study Group between 1985 and 2003.³ Cutaneous involvement was reported in 39% of patients and fever was reported in 45%. Ferreri et al³ also emphasized weight loss and night sweats associated with fever. An exhaustive search for an infectious etiology often contributes to delay in diagnosis.

The main neurologic presentations are multifocal and rapidly progressive neurologic abnormalities. Patients can present with focal sensory or motor deficits, generalized weakness, altered sensorium, rapidly progressive dementia, seizures, hemiparesis, dysarthria, and ataxia.^{1,3,11,12} Initial diagnosis often includes stroke, encephalomyelitis, Guillain Barre syndrome, degenerative dementia, metabolic or infectious encephalitis, neoplasia, vasculitis, and multiple sclerosis.^{2,6,13} Despite the fact that it is very difficult to diagnose IVL during life, it should be suspected in any patient with progressive neurologic dysfunction of unclear etiology.

Cutaneous lesions encompassed a widespread morphology and distribution, including painful and hard erythematous eruptions, poorly circumscribed plaques, swelling overlying skin "peau d'orange," cellulitis, large solitary plaques, painful blue red palpable nodular discolorations, tumor, ulcerated nodules, small red palpable spots, and erythematous and desquamative plaques.³

Pain, mostly associated with cutaneous or abdominal (renal or adrenal) masses, and fatigue are also common presenting symptoms.³ There is no specific laboratory test for IVL. Anemia, elevated lactate dehydrogenase level, leucopenia, thrombocytopenia and elevated erythrocyte sedimentation rate are the most common laboratory abnormalities seen in IVL.^{2,3}

Prognosis is poor especially in patients presenting with neurologic signs. Among the 72 patients with neurologic presentations, only 22 were diagnosed during life.¹² Patients with disease limited to the skin (cutaneous variant) were invariably females exhibiting a significantly better outcome.³

There are no randomized or controlled trials comparing treatments in IVL. Anthracycline-based chemotherapy regimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with the addition of the monoclonal antibody rituximab (R-CHOP) is recommended in cases with a B-cell immunophenotype.² Combination chemotherapy such as m-BACOD (Methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone) or pro-MACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate and prednisone) have been used with varying degrees of success.^{2,3} Cure has rarely been achieved.¹⁴ IVL usually shows rapid progression and short survival, at best with transient remissions. The poor prognosis is often due to delay in diagnosis and initiation of therapy because of their extraordinary presentation. Exceptions are rare cases diagnosed in an early stage of disease.^{14,15}

There are no pathognomonic neuroradiologic findings for IVL. Ischemic foci mostly scattered throughout the cerebral hemispheres are the most common presentation pattern.¹⁶⁻¹⁸ The brainstem and cerebellum are less frequently involved, but our patient had cerebellar infarcts simultaneously with the cerebral ones.¹⁸ MRI findings clearly show the expansion of the infarction sizes and the appearance of new ones in our patient. Expansion of established infarcts, which is relatively uncommon in embolic or thrombotic cerebrovascular disease led us to consider alternate diagnoses. The progression of our patient's neuroradiologic findings paralleled the deterioration of his clinical status.

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Primary angiitis of the central nervous system (PACNS), and to a lesser extent, diffuse systemic necrotizing vasculitis such as polyarteritis nodosa, are the most common differential diagnosis for which a brain biopsy is required for definite diagnosis.¹⁹ Both PACNS and IVL affect small parenchymal and leptomeningeal vessels and result in multifocal ischemic lesions. Constitutional signs and symptoms such as fever, malaise, weight loss, and arthralgias are common in IVL and systemic necrotizing vasculitis, but are usually absent in PACNS.²⁰ Both IVL and PACNS have rapid courses and may respond to corticosteroid therapy but the response is almost always transient and slight in IVL.¹ Although ischemic lesions may occur diffusely throughout the brain in both processes, white matter lesions in CNS vasculitis commonly occur in the deep white matter, and those in IVL often occur in the subcortical and periventricular white matter.^{1,19} Nearly half of the IVL patients with CNS manifestations have cerebral angiography findings consistent with a vasculitic appearance.¹⁸ On the other hand, patients with PACNS may have normal findings on cerebral angiography.^{1,18} There are no markers or noninvasive tests for IVL. A tissue biopsy of the involved organ is the unique antemortem diagnostic tool. Actually our final 2 diagnoses were PACNS and IVL and we could not reach the definitive diagnosis with noninvasive tests. However, the presence of constitutional signs (fever, weight loss, malaise), lesion locations (tendency to have subcortical and periventricular localizations), and normal angiography findings made IVL a more likely diagnosis.

Nearly half of the intravascular lymphoma patients with central nervous system manifestations have cerebral angiography findings consistent with a vasculitic appearance.

Dissemination of IVL is so rapid and extensive that the average survival after antemortem diagnosis is approximately 5 months.⁴ Catastrophic cases have also been described. Our patient, with a 45-day disease course, represents a fulminant case. Combination chemotherapy, if begun early in the course of the disease, may reduce mortality and prolong survival.²¹

Newly appearing lesions, or especially expansion of older subcortical infarcts in imaging studies should draw attention to intravascular lymphoma.

IVL should be considered in the differential diagnosis of unexplained stroke-like syndromes. Progression of clinical findings should alert the clinician to IVL. Newly appearing lesions, or

especially expansion of older subcortical infarcts in imaging studies should draw attention to IVL. A tissue biopsy from an involved organ should be performed and this should be done early if the involved organ is the brain.

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