Diagnosis and Treatment of Intravascular Lymphomatosis

Objective: To describe a patient with unusually good outcome of a rare, high-grade lymphoma that often involves the nervous system.

Design: Case report.

Setting: University hospital.

Case: A 70-year-old pharmacist first presented with meningoencephalitislike symptoms and 6 months later with acute confusional state followed by complex partial status epilepticus. Diagnosis of intravascular lymphomatosis was made using detection and biopsy of a bilateral adrenal tumor.

Main Outcome and Results: Polychemotherapy consisting of CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) led to complete remission. The patient’s survival time currently exceeds 2½ years.

Conclusions: The possibility of intravascular lymphomatosis should be considered in adult patients with unclear meningoencephalitic syndrome, acute confusional state, dementia, or other unexplained neurologic conditions with signs of a systemic disease. In intravascular lymphomatosis, as in other high-grade non-Hodgkin lymphomas, CHOP polychemotherapy should be the standard treatment.

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Intravascular lymphomatosis (IVL), or angiotropic large cell lymphoma, was first described by Pfleger and Tappeiner in 1959 as a cutaneous manifestation of a systemic endotheliomatosis in a young female patient. Proliferating cells were believed to be of endothelial origin, but immunohistochemical studies have shown that the malignant cells bear the immunophenotype of B- or T-cell lineage. Intravascular lymphomatosis is considered to be a rare, high-grade, extranodal non-Hodgkin lymphoma with a tropism for endothelium. The affinity of tumor cells for capillary endothelium may be explained by lymphocyte receptors for endothelial membrane antigens. The disease starts across a wide age range, with a predilection for patients in the seventh decade of life. There is no clear sex difference. The histological characteristic is proliferation of large, atypical lymphoid cells within the lumen of capillaries, small veins, and arteries. The proliferation in the blood vessels of parenchymatous organs results in thrombosis and secondary hypoxic damage. Nervous system and skin have a high incidence of involvement. Infiltration of the lungs, kidneys, adrenal glands, or the prostate is also frequent. All organs may be involved, individually or in combination, but liver, spleen, lymph nodes, and bone marrow are relatively spared until late in the disease. Usually, there are no circulating lymphoma cells in blood or in cerebrospinal fluid (CSF). About two thirds of patients present with neurologic signs, of which diffuse cerebral signs, dementia, or focal cerebral signs have been reported most frequently. Some patients present to a neurologist with myelopathy, peripheral neuropathy, polyradiculopathy, or myopathy. Most cases have been diagnosed only at autopsy because of misleading clinical features mimicking degenerative dementia, vasculitis, stroke, infection, or other neoplasms. Diagnosis can be made by biopsy of the involved organ(s). A variety of therapies has been applied, including chemotherapy and steroid and radiation therapies. Survival time in most patients is less than 1 year. Since IVL often presents with neurologic symptoms and is potentially curable, the diagnosis of this entity is important for neurologists.
A 70-year-old male pharmacist was admitted to the hospital on April 4, 1996, because of fever, headache, vomiting, somnolence, and a generalized seizure beginning with clonic jerks of the right upper limb. He had undergone previous aortocoronary bypass surgery. On examination, no neck stiffness or focal neurologic deficit was present. Routine laboratory tests revealed anemia (hemoglobin level, 10.1 g/L), and the value for C-reactive protein was elevated, increasing from 0.033 to 0.112 g/L. A lumbar puncture was performed. Findings in CSF included an elevated protein level (1.9 g/L) and a slight pleocytosis (20.3 × 10^6 cells) with predominant lymphocytes (0.96 lymphocytes, 0.02 monocytes, and 0.02 polymorphic nucleated cells). Results of cytologic study revealed no malignant cells but suggested an inflammatory process. Cranial computed tomography (CT) and magnetic resonance imaging (MRI) showed no abnormalities, whereas electroencephalography (EEG) showed a moderate to severe generalized slowing of background activity and focal delta activity over left frontotemporal and left parietal areas. Results of serologic tests of the CSF for viruses, Treponema species, and Borrelia burgdorferi and polymerase chain reaction testing for herpes simplex and Mycobacterium tuberculosis were all negative. Acyclovir sodium was given until serologic and polymerase chain reaction results were known. The patient recovered after a few days. He refused further diagnostic procedures and was discharged with an antiepileptic treatment. First diagnosis was meningoencephalitis of unknown origin.

During the next few months, his wife observed loss of energy, memory deficits, and difficulties at work in the pharmacy. He ordered wrong materials, payed bills twice, and had difficulties with reading prescriptions and driving the car, but over time symptoms improved. Six months later, on October 15, 1996, he was readmitted to the hospital because of acute disorientation, difficulties in finding words, and inability to complete sentences. On examination his temperature was 38.2°C, blood pressure was 140/80 mm Hg, and heart rate was 76/min. Mental testing revealed inconstant disorientation in space, time, and surroundings and a reduced digit span. His behavior was changed by an increased drive, fluctuating alertness, agitation, and altered affectivity (first euphoria, later irritability). His speech production was increased and incoherent. He had slight difficulties with naming, reading, writing, and calculation. Encoding and retrieval of a word list was substantially reduced. He showed only minimal abnormalities in copying a complex geometric figure. Mental changes were consistent with delirium according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Routine laboratory tests revealed anemia (hemoglobin level, 11.4 g/L), an elevated C-reactive protein level (0.183 g/L), and an elevated sedimentation rate (66 mm/h). The CSF contained a high protein level (2.7 g/L), but cell count was within the reference range, and results of cytologic studies were normal. No monoclonal protein or adrenal insufficiency was found. Anti-Hu, anti-Yo, or specific antineuronal antibodies were not present. Findings on EEG were similar to those registered 6 months before, showing moderate to severe slow-wave abnormality over both hemispheres and continuous delta activity in left frontotemporal and left parietal regions. The cranial MRI showed a small, hyperintense area in the left posterior lenticular nucleus (Figure 1) with minimal contrast enhancement. There was no contrast enhancement of the meninges and no cortical infarction. Differential diagnosis of the clinical syndrome included paraneoplastic leukoencephalitis. Therefore, a CT scan of the thorax and the abdomen were performed. Bilateral adrenal tumor formations measuring 7 × 3 × 3 cm on the right side and 6 × 5 × 3 cm on the left side were found in combination with multiple lymph nodes in the mediastinum and retroperitoneum that were enlarged up to 2 cm (Figure 2). A CT-guided biopsy of the right adrenal gland was delayed by evolution of a complex partial status epilepticus on October 23, when the patient presented with stupor, lip smacking, and epileptiform discharges on the left temporal side, which resolved under treatment with phenytoin sodium. Finally, results of the biopsy showed adrenal sinusoids filled by noncohesive aggregates of malignant lymphoid cells (Figure 3) with a strong reaction to CD20 antibodies, specific for B lymphocytes. The diagnosis of intravascular lymphoma involving both adrenal glands, brain, and mediastinal and retroperitoneal lymph nodes was made. A CHOP chemotherapy (consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) was started, the last of 8 cycles being administered in March 1997. Clinical, laboratory, and imaging findings improved soon after the first chemotherapy cycle. Apart from a slight sensory polyneuropathy, no neurologic abnormality was found after completion of treatment. Despite mildly el-
Elevated lactic dehydrogenase and ß2-microglobulin levels, the patient is considered to have been in full remission for 34 months after first symptoms or for 28 months after commencement of chemotherapy.

**COMMENT**

A broad spectrum of neurologic syndromes can be seen in patients with IVL, including dementia, delirium, seizures, local neurologic signs, myelopathy, polyradiculopathy, peripheral neuropathy, and myopathy. Diagnosis is usually not made before autopsy because of rapid progression and confounding clinical features mimicking an inflammatory, vascular, or degenerative process that, in the case of central nervous system involvement, suggests meningoencephalitis, cerebral vasculitis, stroke, or dementia. In our patient with an acute confusional state and signs of a systemic illness (fever, elevated sedimentation rate, anemia), diagnosis was reached by considering the possibility of a paraneoplastic syndrome. Definitive diagnosis was made by detection of a bilateral adrenal tumor. Biopsy of this organ presented an alternative to brain biopsy. The nonlocalizing neurobehavioral and EEG findings in our patient probably reflect diffuse infiltration of small cerebral blood vessels, whereas the more focal EEG and the circumscribed MRI changes and changes in the left hemisphere reflect a local maximum of the infiltrative process leading to thrombosis and subsequent infarction visible on MRI and complex partial seizures. Thus, there was a combination of diffuse (or encephalopathic) and local cerebral manifestations. It is not clear whether the amelioration after initial manifestation as a meningoencephalitis was the result of spontaneous transient remission of the lymphoma or recovery from an ischemic event not visible on CT and MRI. In IVL presenting with a neurologic syndrome, CSF studies and brain imaging procedures usually provide unspecific or even normal results. In contrast, the search for enlarged or infarcted visceral organs, as shown in the case report, may be essential to detect the underlying disease. Diagnosis can only be made using biopsy of one of the involved organs, mostly of brain, skin, or lung. Biopsy of a visceral organ, whenever it makes sense, presents an alternative to biopsy of the brain. Although the adrenal gland has been the diagnostic organ in only 1 patient in a survey of 32 with IVL, it is much more common. Bilateral adrenal enlargement was reported in a number of cases and may lead to adrenal insufficiency. Adrenal infiltration was said to be present in 60% of autopsy cases. An abdominal CT scan, therefore, should always be performed in the clinical settings mentioned above. The response to CHOP chemotherapy in our patient was excellent, leading to complete remission and a symptom-free survival time currently exceeding 32 months. Chemotherapy regimens directed at intermediate- and high-grade lymphomas seem to be the most favorable. Although there are no larger case series or randomized studies, the nature of the disease (high-grade lymphoma) and at least 1 patient survey in the literature suggest the use of CHOP chemotherapy for patients with IVL. Of 23 patients receiving CHOP chemotherapy, 6 (55%) of 11 obtained a complete remission. In contrast, response to steroid therapy with or without radiation therapy is probably poor. A transient but dramatic improvement after plasmapheresis has been reported in a patient with IVL and anti–myelin-associated glycoprotein antibodies. Spontaneous remission was observed in a patient with radiographic appearance of cerebral arteritis.

Intravascular lymphomatosis should be considered in the differential diagnosis of unexplained meningoencephalitis, acute confusional state, dementia, or stroke-like syndromes. Investigations should include organs often involved by IVL, such as kidneys, adrenal glands, liver, and lungs. In case of involvement of visceral organs or skin, biopsy of the involved organ may lead to diagnosis without need for a brain biopsy. Treatment with CHOP chemotherapy, as in other high-grade non-Hodgkin lymphomas, should be the standard therapy.

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Figure 2. Axial computed tomographic scan of the upper abdomen showing bilateral adrenal tumors (black arrows) and enlarged retrocrural and para-aortal lymph nodes (white arrowheads).

Figure 3. High-power magnification showing an adrenal capillary filled with a noncohesive aggregate of malignant lymphoid cells (periodic acid–Schiff stain, original magnification ×1120).
REFERENCES


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