Malignant intravascular lymphomatosis associated with venous stenosis

Case report

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This 55-year-old man presented with malignant intravascular lymphomatosis, a rare vascular disorder of the central nervous system characterized by proliferation of malignant lymphoma cells. The clinical manifestations were focal neurological signs and progressive dementia. Angiography demonstrated stenoses of the cortical veins. Postmortem examination revealed infiltration of tumor cells into the lumen and vascular wall, although the stenoses were caused primarily by fibrin thrombi. To the authors' knowledge this is the first case of malignant intravascular lymphomatosis associated with venous stenosis.

KEY WORDS • lymphoma • angiography • venous stenosis • biopsy
Examination. On admission the patient was afebrile, and a general physical examination revealed no abnormalities; no adenopathy or skin changes were seen. There was no deterioration in his neurological deficits. The results of laboratory tests were normal. A cerebrospinal fluid (CSF) study excluded multiple sclerosis. Repeated myelography, CT myelography, and spinal MR imaging performed at our institution 2 weeks after the initial studies revealed similar findings. A microsurgical biopsy of the spine with laminoplasty of T-12 and L-1 was performed to achieve decompression and for histological confirmation of the lesion. Histological examination of the specimen showed degenerative tissue, with no malignant cells or glial changes. The diagnosis was spinal cord infarction. The patient also suffered a few angina attacks, but the results of his cardiovascular studies were normal. There was no deterioration in his symptoms and he was discharged. He complained of persistent headache shortly thereafter, but gadolinium-enhanced MR imaging demonstrated no abnormalities.

One month after discharge the patient was hospitalized again after experiencing a generalized seizure. Computerized tomography scanning revealed no abnormalities. His seizures were controlled with a course of carbamazepine and the results of subsequent electroencephalographic studies were normal. Soon after his second admission to our institution, he was discharged again.

Postoperative Course. Eight months later, he was readmitted with worsening of his gait difficulties and dysuria, slowed thinking and speech, memory disturbance, and general fatigue. Laboratory findings included a lactate dehydrogenase level of 476 IU/L and a C-reactive protein level of 8.15 mg/dl. A CT scan of the patient’s head revealed areas of low density in the white matter of the parietal regions bilaterally (Fig. 2) and single-photon emission CT scanning demonstrated a reduction in cerebral blood flow in the parietal regions on both sides. Digital subtraction angiography revealed no abnormalities in the arterial phase, but did demonstrate stenoses in the cortical veins; therefore, venous thrombosis was suspected (Fig. 3). One month later, the patient’s abdomen began to swell and an abdominal CT scan revealed multiple abnormal lesions in his liver. A biopsy specimen was obtained; on histological examination this proved to be a malignant lymphoma of the B-cell type. The patient’s general condition deteriorated shortly thereafter and he died 18 months following the onset of his symptoms.

Laboratory Studies. Postmortem examination revealed infiltration of tumor cells around the Glisson sheaths, with hemorrhagic changes in the liver. The cerebral white matter contained widespread multiple infarctions consistent with the results of neuroimaging studies. The superior sagittal sinus was partially thrombosed. Enlargement of the lower spinal cord and conus medullaris was observed. Histological studies revealed tumor cells in the vascular wall of the superior sagittal sinus, with deposition of fibrin thrombi (Fig. 4). The cortical veins exhibited deposition of fibrin thrombi, with only a small number of tumor cells in the endothelium (Fig. 5). Many small and medium-sized vessels in the cerebral white matter were filled with tumor cells, including pleomorphic cells with large hyperchromatic nuclei, prominent nucleoli, and scant cytoplasm (Fig. 6).
Immunohistochemical studies of the tumor cells were positive for the B-cell marker L26. The enlarged spinal cord included degenerative nerve cells and was found to have adhered to the dura with revascularization. Small vessels in the nearby dura and nerve roots were infiltrated with tumor cells. Involvement of venules was predominant, which suggested that the infarction was caused by venous occlusion. In addition, tumor cell invasion was discovered in the spleen, kidneys, lungs, heart, bone marrow, adrenal glands, and lymph nodes. The diagnosis was malignant intravascular lymphomatosis.

Discussion

The clinical features of malignant intravascular lymphomatosis include multifocal neurological deficits, with progressive subacute dementia being the most common neurological manifestation. Skin lesions are also of diagnostic significance; these may include asymptomatic erythematous plaques and patches, subcutaneous nodules, and hemorrhagic lesions. The characteristic laboratory findings are increased levels of erythrocyte sedimentation, lactate dehydrogenase, and CSF protein. In most cases malignant cells are not detectable in either the peripheral blood or CSF.

Cerebral CT and MR imaging typically show evidence of multiple vascular occlusions and stroke, especially in the cortical or subcortical areas. Lesions do not usually enhance after administration of contrast agents in either imaging modality, but enhancement of the dura and smaller areas in the cerebral cortex has been reported on MR imaging.\textsuperscript{5,10} In retrospect the CT scan in our case, which demonstrated areas of low density in the white matter regions bilaterally, was a characteristic radiological indication of malignant intravascular lymphomatosis that should have raised the possibility of this disease.

Cerebral angiography is often nondiagnostic, but multiple occlusions or stenoses of medium-sized or small arteries may display an appearance similar to that of vasculitis.\textsuperscript{5,6,11} Angiography in our patient did not reveal abnormalities in the arterial phase, but multiple venous stenoses were demonstrated. Postmortem examination revealed invasion of tumor cells into both arteries and veins, but the bulk of the luminal narrowing was caused by fibrin thrombi. Similar findings on postmortem examination have been reported in the literature,\textsuperscript{1,3,6,11} but angiographic studies have only occasionally detected arterial stenosis. This is the first case of malignant intravascular lymphomatosis associated with venous stenosis.

Proliferation of endothelial tumor may cause regions of occlusion and thrombosis.\textsuperscript{5} On postmortem examination of our patient we found cortical veins with remarkable depositions of fibrin thrombi but only scattered tumor cells. Formation of fibrin thrombi in the endothelium is rare in malignant intravascular lymphomatosis, although vascular lumina packed with tumor cells are often present. These thrombi may have been a result of the patient’s hypercoagulative state, which may have been caused in turn by a change in the surface adhesiveness of the endothelium related to the intraluminal presence of tumor cells;\textsuperscript{5} on the other hand, the thrombi may have formed as a result of disruption of the endothelium by tumor cells. Invasion of endovascular structures by malignant cells sometimes causes endothelial lesions, in which case the relative susceptibility of the vessels at the time may determine whether it is the arteries or the veins that are...
affected (if either type is affected at all). Thus, cerebral angiography only occasionally reveals stenotic lesions. In addition, the angiographic appearance of vessels may change during the course of the disease. In one reported case, results of angiography were initially normal but later revealed multiple areas of stenosis or occlusion. Repeated angiography or MR angiography may be helpful in detecting vascular lesions. In our case, MR venography might have been useful in detecting sinus involvement.

Because of the rarity of the disease, the relative merits of therapeutic interventions have not been thoroughly evaluated. Administration of corticosteroid medications alone or in combination with chemotherapy with or without radiation therapy has been attempted, but with unsatisfactory outcomes. Delay in the diagnosis may reduce the effectiveness of the treatment; thus, early diagnosis is of paramount importance for successful management.

Although malignant intravascular lymphomatosis is rare, it should be considered as a possible diagnosis in any patient who presents with progressive neurological symptoms. Close examination of the laboratory and neuroimaging findings should be followed by biopsy of the brain, meninges, or other regions affected by lesions if these are present, especially when neuroimaging reveals multiple white matter lucency and abnormal vessel narrowing. Increased awareness of this disease will most likely lead to the discovery of more cases on premortem examination.

References


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