Intravascular lymphomatosis presenting with a conus medullaris syndrome mimicking disseminated encephalomyelitis

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We describe the clinical, radiologic, and postmortem findings of a 42-year-old man with intravascular lymphomatosis. The patient presented with a conus medullaris syndrome followed by progressive, disseminated spinal and cerebral symptoms. Disseminated encephalomyelitis was suspected due to the clinical, radiologic, and cerebrospinal fluid findings and the results of a stereotactic brain biopsy, all of which were compatible with inflammatory CNS disease. Treatment with methylprednisolone and cyclophosphamide led to a temporary remission of symptoms. The patient died 13 months after onset of symptoms. The diagnosis of disseminated intravascular lymphomatosis was established after death. *Neuro-Oncology* 4, 187–191, 2002 (Posted to *Neuro-Oncology* [serial online], Doc. 01-058, April 5, 2002. URL <neuro-oncology.mc.duke.edu>)

Intravascular lymphomatosis is a rare, multifocal non-Hodgkin lymphoma, most commonly of B-cell lineage, with exclusively or predominantly intravascular proliferation in the capillaries, venules, arterioles, and small arteries (Baumann et al., 2000; Chapin et al., 1995; Demirer et al., 1994). The disease predominantly affects the vessels in the skin and in the central and peripheral nervous system, although virtually any other organ may be involved and may produce a variety of clinical findings (Demirer et al., 1994; Glass et al., 1993).

Most patients with intravascular lymphomatosis are diagnosed after death (Demirer et al., 1994; Glass et al.,

1993). Without therapeutic intervention, the neurologic involvement is usually rapidly progressive and inevitably fatal. There are now several reports suggesting that an aggressive therapy may be beneficial and, therefore, an early diagnosis is probably crucial for patient outcome (Baumann et al., 2000; Harris et al., 1994; Levin and Lutz, 1996; Nakahara et al., 1999). We report on a patient with intravascular lymphomatosis and with symptoms limited to the CNS. Bone marrow and brain biopsy were negative for malignancy, and the clinical and radiologic findings mimicked disseminated encephalomyelitis.

Case Study

A 41-year-old factory worker presented with fatigue, perianal and genital sensory loss, urinary incontinence, and erectile impotence of increasing severity for 3 weeks. He had no history of medical problems, and he had not had an infection or been immunized in the weeks before presentation. Initial examination revealed a conus medullaris syndrome with sensory loss over the sacral dermatomes, a lax anal sphincter with loss of anal and bulbocavernosus reflexes, fecal constipation, and urinary retention. The general medical examination was unremarkable. The patient was not febrile, and electrocardiogram and chest X-ray were normal. T2-weighted images of the lumbar spinal cord revealed a hyperintense lesion within the conus medullaris (Fig. 1) that enhanced after administration of gadolinium-diethyltri-*n*-methylpentacetic acid. Cranial T2-weighted and fluid-attenuated inversion recovery (FLAIR) images showed several nonenhancing hyperintense lesions in the subcortical white matter and in association with the corpus callosum. The CSF² had 1.1 g/liter protein and 61 leukocytes/microliter; cytologic studies showed 90% lymphocytes, 5% monocytes, and a

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²Abbreviations used are as follows: CSF, cerebrospinal fluid.

Fig. 1. T2-weighted MRI of the lumbar spinal cord showing a hyperintense lesion within the conus medullaris, which diffusely enhanced after administration of gadolinium-diethyltriaminepentaacetic acid (not presented here).

few plasma cells. The ratio of the CSF and serum albumin was elevated (14.7), indicating a disturbance of the blood-brain barrier. There were no CNS-specific oligoclonal bands and no intrathecal production of immunoglobulins. The CSF was evaluated using polymerase chain reaction-based, automated, high-resolution fragment analysis of rearranged immunoglobulin heavy-chain genes as previously described (Wildemann et al., 2001). Analysis revealed a polyclonal B-cell response further supporting the diagnosis of inflammatory disease. After this finding, further immunocytochemical analyses were not performed. Other CSF parameters, including those from an extensive microbiologic work-up, were normal. Routine laboratory data—including differential blood cell count, lactic acid dehydrogenase, and various parameters for infection, vasculitis, and autoimmune diseases—were unremarkable. Bone marrow histology with immunohistochemical analysis of the sediment also disclosed no abnormalities. Arteriography of the cerebral arteries was normal except for a sudden stop of the contrast medium in the distal right paracentral artery, a showing that was considered an unspecific abnormality. With these findings, the presumed diagnosis of acute inflammatory demyelinating disease of the CNS was established, and treatment with methylprednisolone i.v. (0.5 g/day over 5 days) was initiated. Immediately after the treatment with methylprednisolone, the CSF results improved dramati-

cally (4 leukocytes/microliter; protein 0.7 g/liter). Clinically, the symptoms remained unchanged, and the patient was discharged on oral methylprednisolone, which was tapered over the next 3 weeks.

Three weeks after discharge, the patient presented again with progressive symptoms. In addition to the conus medullaris syndrome, he now had moderate paraparesis and fecal incontinence. Spinal MRI was repeated and showed an enlargement of the intramedullary lesion. New lesions were found on the cranial MRI (Fig. 2). CSF showed an elevated protein content (1.1 g/liter) and lymphocytic pleocytosis (42/microliter). CNS-specific oligoclonal bands were now detectable. Treatment with i.v. methylprednisolone (0.5 g/day over 5 days) was repeated, but again, was not effective in improving the neurologic deficits. The patient rapidly became paraplegic. Secondary generalized seizures were treated with carbamazepine, and interval therapy with cyclophosphamide (1 g i.v. every 4 weeks) was initiated. Under this therapy, clinical symptoms as well as CSF parameters and radiologic findings improved slightly, and cyclophosphamide therapy was stopped after a total dosage of 6 g. After cyclophosphamide therapy was discontinued, the clinical, CSF, and radiologic findings deteriorated rapidly. The patient was constantly confused, showed severe attention and memory deficits, and required constant help in all activities of daily living. To exclude other autoimmune and infectious diseases or lymphoma, an extensive search was performed again, including various laboratory tests for autoimmune diseases and vasculitis, a repeated bone marrow biopsy, whole-body leukocyte scintigraphy, and abdominal ultrasound. All test results were normal except for a mildly enlarged spleen on abdominal ultrasound. A CT-guided stereotactic brain biopsy of a single frontal contrast-enhancing lesion was performed. Smear preparations and paraffin-embedded sections demonstrated predominantly gray matter with reactive astrocytes and a small number of lymphocytic infiltrates with a predominance of CD45RO-positive T cells, giving further support for the diagnosis of inflammatory disease. Immunocytochemistry for CD68 did not reveal macrophages or microglial cells. A postoperative cranial MRI revealed that the actual biopsy site was the lesion that had been targeted. The biopsy consisted of 5 tissue fragments and was considered an adequate biopsy. Therapy with cyclophosphamide was started again but could not halt the rapidly progressive deterioration. The patient developed delirium with agitation, hallucinations, and progressive dementia. He died 2 months later after a series of generalized seizures, 13 months after the onset of symptoms.

Postmortem sections of the brain showed multiple, acute hemorrhagic cortical infarcts in all lobes and in the cerebellum. Chronic infarction was present in the left parietal lobe. Acute ischemic necrosis was seen in the subcortical white matter of both parietal lobes and adjacent to the lateral ventricles. Sections of the spinal cord demonstrated multiple small hemorrhagic necroses in thoracic and lumbar segments, a condition that was accentuated in the gray matter. Microscopic examination revealed the cause of vascular occlusion and consecutive infarcts: middle-sized and small intracerebral and leptomeningeal blood vessels were plugged by thrombus-like masses of densely packed neoplastic cells with a high

Fig. 2. Cranial MRIs. A. T2-weighted image showing several hyperintense lesions located in the subcortical white matter and partly involving the adjacent cortex. B. T1-weighted image after administration of gadolinium-diethyltriaminepentaacetic acid. Some of the lesions show diffuse enhancement. C. Seven months later, T2-weighted image revealing multiple hyperintense lesions, mostly located in the subcortical white matter, with and without contrast enhancement (not shown here).

nucleus/cytoplasm ratio and well-defined cytoplasmic boundaries (Fig. 3). The eosinophilic cytoplasm ranged from scant to moderate. The nuclei were large with moderate chromatin density, and cells contained one or more distinct nuclei. The tumor cells showed no cellular cohesion, and mitotic configurations were common. Occasionally, tumor cells spilled over into the cerebral parenchyma. Similar tumor cells were found in the small vessels of the spinal nerve roots. Immunohistochemically, the tumor cells were positive for the B-cell-associated antigen CD20. Examination of the peripheral organs also showed intravascular neoplastic cells in the kidneys, liver, and adrenal gland. The histologic and immunohisto-

chemical findings were consistent with angiotropic large B-cell lymphoma according to the revised European-American classification of lymphomas (REAL) (Isaacson, 1995).

Discussion

We report on a patient in whom intravascular lymphomatosis was misdiagnosed intra vitam as disseminated encephalomyelitis even though numerous diagnostic procedures were conducted, including several lumbar punctures, extensive radiologic examinations, repeated bone

Fig. 3. Photomicrographs of intravascular neoplastic cells stained with an antibody against B-cell-associated CD20 (L26). A. Two blood vessels (arrows) located in the region of a spinal root and having tightly packed intraluminal tumor cells. Original magnification $\times 100$. B. At higher magnification, showing a mitotic figure (arrow). Original magnification $\times 400$.

marrow biopsy, and a stereotactic brain biopsy. The clinical and radiologic findings were atypical for disseminated encephalomyelitis. However, there is a wide variety of subforms in the heterogeneous range of demyelinating CNS diseases, and large, tumor-like manifestations of disseminated encephalomyelitis have been described repeatedly (Kepes, 1993). There are no generally accepted diagnostic criteria for disseminated encephalomyelitis and, therefore, we use the term as a description of a clinical syndrome (Hartung and Grossman, 2001; Schwarz et al., 2001). Clinical, CSF, and radiologic findings, as well as the results from the brain biopsy, were all compatible with the diagnosis of disseminated encephalomyelitis. Therefore, the only findings that might have hinted at the correct diagnosis, in retrospect, were the minimal changes on cerebral arteriography, which were considered insignificant at the time.

Although intravascular lymphomatosis can affect virtually any organ, most patients have, for unknown reasons, prominent or exclusive manifestations in the nervous system (Chapin et al., 1995; Demirer et al., 1994; Glass et al., 1993). As in our patient, bone marrow involvement and leukemia are rare (Tucker et al., 1999).

In intravascular lymphomatosis, the CSF typically shows lymphocytic pleocytosis and elevated protein content, which usually prompt the primary diagnosis of inflammatory disease (Glass et al., 1993). CSF cytology is usually negative for malignancy; there have been only a few case reports of neoplastic cells found in the CSF (Ossege et al., 2000). In our patient, CNS-specific oligoclonal bands became detectable during the clinical course, further supporting the misdiagnosis of disseminated encephalomyelitis.

Neurologic symptoms result from occlusion of the small vessels with subsequent hypoxia and ischemic infarcts and are typically multifocal and highly variable. In contrast to disseminated encephalomyelitis, dementia, aphasia, seizures, and psychosis are frequent findings (Demirer et al., 1994; Glass et al., 1993). Typically, the spinal cord seems to be involved, and there are several reports of patients who presented with spinal symptoms (Hamada et al., 1991; Levin and Lutz, 1996; Nakahara et al., 1999; Ojeda, 1983; Ossege et al., 2000). However, an isolated conus medullaris syndrome as the presenting syndrome has not been described until now.

Because signs of systemic involvement may appear only in the final stage of the disease and there are no specific radiologic findings, a brain biopsy is usually diagnostic for intravascular lymphomatosis if systemic involvement is absent (Demirer et al., 1994; Glass et al., 1993). However, as our case demonstrates, even stereotactic biopsy can miss the correct diagnosis because of sampling errors.

Treatment with cortisone alone does not seem to be effective (Fredericks et al., 1991; Ossege et al., 2000). In our patient, interval therapy with cyclophosphamide obviously halted disease progression. Untreated, the prognosis is very poor with an almost invariably fatal course within 1 year (Demirer et al., 1994). When various high-dose chemotherapy regimens are used, a significantly better prognosis has been reported if the diagnosis of intravascular lymphomatosis was established early in the disease (Demirer et al., 1994; Glass et al., 1993; Levin and Lutz, 1996; Nakahara et al., 1999). Therefore, intravascular lymphomatosis should be included in the differential diagnosis of every atypical case of presumed myelitis, including conus medullaris syndrome or disseminated encephalomyelitis.

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