A 62-Year-Old Man With Fluctuating Neurological Deficits and Skin Lesions

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A 62-year-old man with no significant medical history experienced fatigue, night sweats, hoarseness of voice, and dry cough, which were followed by vision disturbances in his left eye. He lost about 4.5 kg (10 lb) in just over a month. Three weeks later, he had difficulty recollecting his e-mail password and trouble with word finding. The next day, he experienced numbness in his left arm. He also developed a maculopapular and erythematous rash in the groin, genitalia, and buttocks. The results of an initial neurological examination were normal, including his higher mental functions. An initial blood workup revealed normocytic normochromic anemia. The results of cerebrospinal fluid studies were unremarkable. Magnetic resonance imaging of his brain at hospital admission revealed multifocal increased T2 signals in the subcortical white matter. A conventional cerebral angiogram was unremarkable. A biopsy specimen from the right frontal lobe revealed demyelination and perivascular lymphocytic infiltration. A provisional diagnosis of acute disseminated encephalomyelitis was made. In spite of steroid treatment and plasmapheresis, his clinical status deteriorated rapidly. The approach to the diagnosis of a rapidly progressive multifocal brain disorder is discussed.


A previously healthy 62-year-old man experienced fatigue, night sweats, hoarseness of voice, and dry cough. He also noted vision disturbances in his left eye, which consisted of seeing circles and halos. He lost about 4.5 kg (10 lb) in just over a month. He was evaluated by his primary care physician, an ophthalmologist, an otolaryngologist, and an oncologist. He was told that he had “retinal edema” and was prescribed oral steroids for a few days. The results of computed tomography of the chest and abdomen were unremarkable. The results of laboratory studies revealed normocytic normochromic anemia. The patient underwent biopsies of a cervical lymph node and of bone marrow; the results from both were normal. Three weeks later, he experienced an episode of confusion that lasted 12 hours and that consisted of difficulty recollecting his e-mail password and trouble with word finding. The next day, he experienced numbness in his left arm. He was admitted to our hospital for evaluation 25 days after the onset of the first visual symptoms.

He reported no significant medical history other than chronic herpes simplex virus 2 infection. His family history was significant for carcinoma of the stomach in his mother. He denied tobacco or alcohol use.

On admission, his vital signs were normal. On examination, he was in no distress but appeared pale. The results of cardiovascular, pulmonary, and abdominal examinations were unremarkable. There was no lymphadenopathy. Maculopapular and erythematous lesions were noted in the groin, genitalia, and buttocks. A neurological examination revealed normal at-

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tention, comprehension, speech, language, and memory. The results of a cranial nerve function examination and a fundoscopic examination were normal. His reflexes were normal and symmetric, and his plantar reflexes were flexor. The results of motor, sensory, and cerebellar examinations were normal.

The day after admission, the patient had a seizure-like episode, which consisted of a staring spell followed by progressive worsening of confusion. Over the next few days, his mental status deteriorated. Electroencephalograms revealed generalized delta-theta slowing, and one of the electroencephalograms showed intermittent generalized sharp waves with left-sided predominance. Treatment with levetiracetam was started.

Based on imaging findings, a provisional diagnosis of acute disseminated encephalomyelitis was made. Intravenous methylprednisolone acetate (250 mg, 3 times a day) was administered for 9 days without response. He became increasingly less responsive. He then received 5 daily plasma-exchange treatments for refractory inflammatory demyelinating disease, but this did not result in any improvement. The patient’s hospital course was complicated by the development of an upper gastrointestinal bleed and thrombocytopenia. Ultimately, the patient became comatose. His family elected to provide comfort measures, and he died 48 days after hospitalization.

LABORATORY AND RADIOLOGICAL DATA

On admission, laboratory studies showed a normal white blood cell count with a normal differential count. His hemoglobin level was 8.7 g/dL (to convert to grams per liter, multiply by 10), with a mean corpuscular volume of 88.2 μm² (to convert to femtoliters, multiply by 1.0). He had a platelet count of 196 × 10³/μL (to convert to ×10³/L, multiply by 1.0), a lactate dehydrogenase level of 312 U/L (to convert to microkatal per liter, multiply by 0.0167), an erythrocyte sedimentation rate of 120 mm/h, and a C-reactive protein level of 8.8 mg/L (to convert to nanomoles per liter, multiply by 9.524). The results of renal and liver function tests, including coagulation studies, were normal. His lipid profile was unremarkable. His vitamin B₁₂, folic acid, thyrotropin, and ammonia levels were normal. The results of hepatitis A, B, and C and human immunodeficiency virus serologies were negative. The results of West Nile virus, Epstein-Barr virus, and Lyme disease serologies were negative. Anti-La, anti-Ro, antiphospholipid, antcardiolipin, and anti-Purkinje cell antibodies were negative. Thyroid peroxidase antibody titer was elevated at 73.5 U/mL. Serum immunofixation revealed no monoclonal gammopathy. Blood and urine culture results were negative.

Samples of his cerebrospinal fluid (CSF) were clear in appearance, and he had a white blood cell count of 6 cells/μL (to convert to grams per liter, multiply by 0.001), a red blood cell count of 37 cells/μL, a glucose level of 63 mg/dL (to convert to millimoles per liter, multiply by 0.0555), a protein level of 42 g/dL (to convert to grams per liter, multiply by 10.0). His Venereal Disease Research Laboratory test for syphilis was nonreactive, and his angiotensin-converting enzyme level was normal. He tested negative for cryptococcal antigen, and he tested negative for enterovirus and herpes simplex virus 1 using polymerase chain reaction. His CSF (bacterial, fungal, and acid-fast bacilli) culture results were negative. The CSF results from flow cytometry were unremarkable.

Magnetic resonance imaging (MRI) of the patient’s brain at hospital admission revealed multifocal increased T2 signals in the subcortical white matter (Figure 1A) and central pons. No restricted diffusion or contrast-enhancing lesions were seen. The results of an MRI of the cervical, thoracic, and lumbar spine were unremarkable.

One week later, the results of another MRI revealed worsening of subcortical lesions and the appearance of new cortical lesions, areas of restricted diffusion (Figure 1B), hypointense lesions in the gradient echo sequences (Figure 1C), and a subtle contrast-enhancing lesion in the left temporal lobe (Figure 1D). A biopsy of the right frontal lobe showed demyelination (E; Luxol fast blue/PAS stain for myelin with hematoxylin-eosin [original magnification ×10]) and perivascular lymphocytic infiltration (F; hematoxylin-eosin [original magnification ×20]).
infiltration (Figure 1F), but no evidence of neoplastic cells. Of note, the biopsy specimen was obtained after the patient had received 8 days of intravenous steroids.

**CLINICAL COMMENT**

The salient features of this case are prominent constitutional symptoms and subacute progressive neurological deterioration with multifocal subcortical brain lesions, skin lesions, and lack of therapeutic response to steroids and plasmapheresis.

The differential diagnosis of a subacute multifocal disease of the central nervous system (CNS) is broad, including inflammatory, infectious, metabolic, autoimmune, and neoplastic conditions. However, the presence of weight loss, night sweats, anemia, and elevated inflammatory markers and the paucity of other positive findings from blood and CSF samples limit the most likely diagnostic categories to systemic illnesses that may predominantly affect the CNS.

Even though seldom seen in patients who test negative for human immunodeficiency virus, primary CNS lymphoma and progressive multifocal leukoencephalopathy need to be considered. Similarly, paraneoplastic limbic encephalitis, gliomatosis cerebri, and multiple CNS metastases from a systemic cancer are also unlikely based on the MRI and biopsy findings. Herpes simplex encephalitis is unlikely given the protracted presentation and the absence of CSF findings and characteristic imaging findings.

With evidence of demyelination from the biopsy specimen, a fulminant primary demyelinating disorder, such as a hemorrhagic variant of acute disseminated encephalomyelitis, is a consideration, even though it is more common in children. Other primary demyelinating disorders, such as multiple sclerosis and its variants, are not supported by the patient’s history or clinical syndrome.

The demyelination found in the pathologic specimen may also be a feature of ischemic brain pathology, particularly in microangiopathic disease.Binswanger disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy could be considered, but these are unlikely given their acute presentation, rapid progression, and lack of other diagnostic features. A hypercoagulable state, associated with malignancy or autoimmune disorder causing multiple infarcts, may be a consideration, but there is no supporting laboratory evidence.

The perivascular inflammation seen in the brain biopsy specimen and associated skin findings suggest an inflammatory vasculopathy not limited to the brain. Dermatological findings are associated with several unusual cerebrovascular syndromes, including malignant atrophic papulosis, Sneddon syndrome, and Fabry disease, but the lesions in this case are different, and our patient lacks other pathognomonic features. Lymphomatoid granulomatosis, Wegener granulomatosis, and Behçet disease are also unlikely given the lack of pulmonary and other organ involvement. Intracranial granulomatous arteritis and primary CNS vasculitis are possible because the sensitivity of a conventional angiogram varies between 27% and 90% in these cases, and a biopsy will fail to show diagnostic lesions in 25% of cases owing to patchy involvement.

Vasculitis associated with systemic lupus is unlikely given the age at onset and the lack of serological markers. Hashimoto encephalopathy is possible given the elevated anti–thyroid peroxidase antibody titer and perivascular infiltrates, but this is characteristically a steroid-responsive condition. Indeed, some have proposed that steroid responsiveness is a required feature for this clinical diagnosis. Neurosarcoidosis is possible but unlikely given the absence of systemic involvement, CSF abnormalities, or biopsy findings.

The most likely differential diagnoses based on the clinical course, imaging findings, and biopsy specimens are acute disseminated encephalomyelitis, primary or secondary CNS vasculitis, and primary or secondary CNS lymphoma. Demyelination may be seen in any inflammatory condition and, therefore, does not necessarily point to a primary CNS demyelinating disorder. Perivascular lymphocytic infiltration may be seen in acute disseminated encephalomyelitis, vasculitis, or CNS lymphoma. The systemic symptoms (weight loss, fever, and fatigue) can also be a feature of any of these 3 diagnoses. A negative result for an angiogram does not exclude CNS vasculitis.

**NEUROPATHOLOGY**

An autopsy restricted to the brain revealed multifocal necrotizing and ischemic infarctions of the cerebral cortex and white matter in the gross specimen. Microscopy revealed intravascular lymphoid cells with marked cytopathic atypia and some endothelial proliferation (Figure 2A and B). These cells were almost exclusively B lymphocytes based on the immunohistochemical staining for CD20, CD79a (Figure 2C), and PAX5 (Figure 2D) cellular markers. These intravascular lymphocytes were distributed in the cerebrum, cerebellum, brainstem, choroid plexus, and leptomeninges. There were areas of recent ischemic necrosis, hemorrhage, and spongiosis (Figure 2E and F). These findings were consistent with intravascular large B-cell lymphoma (IVLCL). A retrospective analysis of the brain biopsy failed to reveal atypical lymphocytes. The biopsy had initially revealed a mixed population of CD20-positive B cells and CD3-positive T cells, but reanalysis showed a predominance of CD20-positive intravascular cells in only 1 block. The frozen section failed to show selective staining or atypia. Staining for Epstein-Barr virus was performed for the biopsy and autopsy specimens, and they were negative for the virus.

**SUMMARY**

Intravascular lymphoma was first reported in 1959 by Pfleger and Tappeiner. They named it angioendotheliomatosis proliferans systematica because the malignancy was thought to be of endothelial origin. A lymphoid origin was suggested by Ansell et al in 1882 and was confirmed by Wick et al in 1986. Pathologically, IVLCL can be defined as an extranodal non-Hodgkin lymphoma characterized by malignant proliferation of lymphoid cells within the lumens of small- to medium-size blood vessels.
sized blood vessels.\textsuperscript{1,2} To our knowledge, there have also been few case reports of IVLBCL involving large blood vessels.\textsuperscript{2} The cells are large, with mitotic figures and prominent nucleoli.\textsuperscript{1} There is still a debate about the origin of these cells; some postulate that they have their origin in postgerminal center cells, and others believe that they have their origin in germinal center cells.\textsuperscript{1} The cells are primarily found in capillaries in the CNS and skin.\textsuperscript{1} Sinusoidal or capillary involvement of the liver, spleen, bone marrow, kidney, prostate, uterus, gastrointestinal tract, thyroid, adrenal gland, and pituitary gland are common.\textsuperscript{1,2} Another characteristic is minimal extravascular/parenchymal involvement, and therefore lymphadenopathy is usually absent.\textsuperscript{1} The presence of tumor cells in the peripheral blood and CSF is very rarely seen.\textsuperscript{1}

Immunophenotyping reveals that 85% to 90% of cases of IVLBCL have their origin in B cells and that 10% to 15% of cases of IVLBCL have their origin in T cells; rarely are natural killer cells the origin.\textsuperscript{3} Most B cells express CD19, CD20, CD22, CD79a, and PAX5. An important characteristic is that they express low levels of CD29 (\(\beta_1\) integrin), CD54 (intracellular adhesion molecule 1), CD18, and matrix metalloproteinases 2 and 9, which are required for transvascular trafficking.\textsuperscript{4-6} This results in intravascular confinement. The high endothelial venules, through which the normal transvascular migration of lymphocytes occurs, are few in number or absent in the CNS and skin.\textsuperscript{4} This further explains why the cells are found in capillaries. Cytogenetic studies have revealed aberrations in chromosomes 1, 6, and 18.\textsuperscript{1}

There are 2 major phenotypic variants described so far.\textsuperscript{1,2} The Western or European variant can be found in the CNS and skin (combined, 68% of cases), and the Asian variant is characterized by hemophagocytosis (59% of cases).\textsuperscript{1,4,7} Based on an Asian cohort, the male to female incidence ratio is approximately 1.3, and median age for those who have the cells is 67 years; based on a European cohort, the male to female ratio is 0.9.\textsuperscript{1,8} There is a hypothesis that differences in the production of inflammatory cytokines like IFN-\(\gamma\), tumor necrosis factor, IL-1\(\beta\), and soluble IL-2R result in ethnic difference.\textsuperscript{1}

In a cohort study by Shimada et al\textsuperscript{1} of 106 Asian patients, 59% had clinical manifestations of hemophagocytosis. Only 25% had neurological symptoms at the initial presentation.\textsuperscript{1} Patients showed increased levels of lactate dehydrogenase, soluble IL-2 receptors, and C-reactive protein; the presence of anemia, thrombocytopenia, hypoa-lbuminemia, and leukocytopenia; and elevated levels of bilirubin and creatinine.\textsuperscript{1} In a European cohort study\textsuperscript{8} of 38 patients, 15 (39%) presented with cutaneous manifestations as the dominant symptom, and it was the exclusive presenting symptom in 10 of the 38 patients (26%). In the European cohort study,\textsuperscript{8} 13 patients (34%; compared with 27 patients [25%] in the Asian cohort study\textsuperscript{1}) presented with neurological symptoms that were the sole presenting symptoms for 5 patients (13%). The laboratory findings were similar to those of the Asian cohort study.\textsuperscript{1} The most common symptoms in both populations included nonspecific symptoms such as fever, fatigue, night sweats, and altered mental status.\textsuperscript{1,3} Other clinical presentations described in the literature include pulmonary hypertension and embolism, renal involvement, hepatosplenomegaly, cystitis, prostatic hypertrophy, and endocrinopathies from pituitary, adrenal, and thyroid involvement.

Biopsies of the brain, skin, bone marrow, kidney, liver, and prostate; uterine cytology; and a transbronchial biopsy may all help in confirming the diagnosis.\textsuperscript{1,8,9} Skin biopsy specimens are taken from multiple sites.\textsuperscript{1,9} The location of the skin lesions should determine the site of a biopsy.\textsuperscript{9} In the Asian cohort study,\textsuperscript{1} 13 patients without skin manifestations were determined to have tumor cells with skin involvement.\textsuperscript{1} In the Asian phenotype, bone marrow is an important diagnostic site, and often repeated studies are needed.\textsuperscript{1}

The results of an MRI are often nonspecific. It usually reveals multiple subcortical white matter lesions in T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted imaging sequences.\textsuperscript{2,10} Diffusion restriction is seen in the acute phase and after gadolinium enhancement in the subacute phase.\textsuperscript{2,10} Hypointense lesions in gradient echo sequences suggest hemorrhage.\textsuperscript{10} Linear T2-weighted hyperintensities in a vascular pattern may occasionally be seen.\textsuperscript{10} A conventional cerebral angio
gram might show evidence of vasculitis, but it very rarely happens. Fludeoxyglucose F18 positron emission tomography is nonspecific, even though some studies have shown it to be helpful.10

Half of the patients are diagnosed after autopsy.8 Survival without chemotherapy is about 3 months.1 The mean (SD) 3-year survival rate with CHOP chemotherapy alone (ie, cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone) was 33% (11%).8 The overall survival rate with chemotherapy and rituximab ranged from 60% to 81% at 3 years, based on 2 different studies.1,2

CONCLUSIONS

In our patient, the correct diagnosis was not reached despite a brain biopsy. The working diagnosis based on the results of the biopsy was acute disseminated encephalomyelitis. Prior steroid therapy and a small biopsy specimen might have led to the lack of correlation with the autopsy. It is not unusual for the malignant cells to evade the peripheral blood, bone marrow, and CSF. The patient’s skin lesions may have been a manifestation of the disease, and a skin biopsy might have improved the diagnosis. Because malignant cells can invade any organ system, including the CNS, the presentation is variable, and the diagnosis is often challenging.

Intravascular lymphoma may be considered in an elderly patient presenting with diffuse and focal neurological symptoms along with systemic manifestations, especially hemophagocytosis and skin lesions. We would like to emphasize the importance of skin biopsies from multiple sites and repeated bone marrow biopsies in cases for which intravascular lymphoma is a consideration. Biopsies from other organs may also be considered depending on the presentation. We suggest withholding steroid therapy if intravascular lymphoma is a consideration.

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