Subarachnoid hemorrhage in a patient with Lyme disease

Article abstract—Neuroborreliosis can cause a wide variety of seemingly unrelated neurologic abnormalities. Although the epidemiology, etiology, and pathology of this infection have been well documented, the pathogenesis and diagnosis continue to be problematic. In the current study we report a case of Lyme disease in which subarachnoid hemorrhage was the presenting feature of a patient with polyradiculoneuropathy and encephalopathy. Magnetic resonance imaging of the spine demonstrated diffuse pial and meningeal enhancement with more focal nodular areas of involvement.

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Over the last decade, the rising incidence of Lyme disease has been associated with an increasing variety of clinical manifestations. In North America, infection by *Borrelia burgdorferi* is transmitted from an animal reservoir to humans through the bite of the ixodid tick. Infection reflects three disease stages.[1,2] Stage 1 occurs within a month of inoculation and is associated with a characteristic rash (erythema migrans), fever, fatigue, malaise, headache, stiff neck, arthralgia, and myalgia. Within 2 to 3 months of the initial infection, 10% of untreated patients develop more disseminated disease of the nervous system and heart, producing aseptic meningitis, encephalitis, cranial nerve palsies, and peripheral neuropathies, as well as congestive heart failure. Stage 3 is manifested by arthritis with chronic neurologic and neuropsychiatric syndromes resulting from progressive encephalomyelitis, polyneuritis, or both. This late stage may occur in the absence of a prior clinical disease.[1-3] The range of clinical presentation can make diagnosis obscure. MRI findings are most commonly limited to nonenhancing lesions in the subcortical white matter of the frontal lobes, periventricular area, and brainstem.[4] Isolated meningeal involvement is rare and spinal cord MRI is usually normal.[5] To the best of our knowledge, this is the first report in the literature demonstrating subarachnoid hemorrhage (SAH) as a complication of Lyme disease.

Case Report. A 25-year-old previously healthy woman from Maryland's Chesapeake Bay area presented with a 2-month history of progressive refractory occipital headaches and migratory arthralgias of the right upper extremity. She had extensive exposure to ticks and recalled multiple tick bites, the last of which occurred approximately 6 weeks prior to onset of her headache. Two weeks prior to presentation, she was treated with prednisone for urticaria and dyspnea, following nitrofurantoin treatment of a urinary tract infection. Five days prior to admission, lower extremity distal paresthesias and weakness had progressed to include her arms, and she developed severe midline lumbosacral pain, nausea, and vomiting.

Her examination showed meningismus, bifacial paresis (R>L), decreased gag, 4/5 strength in proximal upper extremities, and 2/5 proximally in the legs. Reflexes were intact in the upper extremities but absent in the legs. Proprioception and vibratory sense were initially preserved. CSF obtained from two initial lumbar punctures performed at another hospital was grossly hemorrhagic, containing a neutrophilic pleocytosis as well as increased protein and normal glucose (table). Initial MRI examination performed within 1 hour of CSF examination demonstrated diffuse pial enhancement along the entire cord surface that was greatest at the level of the conus and lumbar region (figure 1A). Intrathecal nerve roots were thickened and a focal nodular area of intradural/extramedullary enhancement occurred along the right side of the thecal sac at the T-12-L-1 level (figure 1, B and C). Electrophysiologic testing indicated a multifocal process with conduction block involving the median, ulnar, and peroneal at the left wrist, elbow, and knee. There was no temporal dispersion of the compound muscle action potentials. Distal latencies were mildly prolonged in the median nerve, and velocity was reduced in the left ulnar nerve. F waves were absent throughout.

The patient's subsequent clinical course was complicated by acute anaphylactic shock to ceftriaxone given empirically for CSF pleocytosis. Treatment was switched to chloramphenicol and trimethoprim sulfamethoxazole. Following plasma exchange, initiated for treatment of possible Guillain-Barré syndrome, her headache, photophobia, nausea, vomiting, and back pain dramatically worsened and CSF blood increased (see table). Head CT was unremarkable. Cerebral angiography did not reveal any AVM or aneurysm. The patient experienced continued weakness and pain with a rapid deterioration in mental status associated with acute SIADH and a generalized seizure. She developed an acute left sixth and seventh nerve palsy with a marked lability of affect and child-like personality. Following aggressive restabilization, MRI of head with gadolinium revealed diffuse leptomeningeal enhancement. The nodular intradural/extramedullary focus along the thecal sac at T-12-L-1 showed increased T_1 and diminished T_2 signal intensity, compatible with methemoglobin (figure 2). EEG did not reveal any epileptogenic foci. CSF culture and cytology was negative. She was anergic on skin testing. Chest and abdominal CT as well as pulmonary function studies were normal. A reactive ANA titer of 650 had a

Table *Patient data*

Day	0	1	5	8	19
Clinical course	Headache/Weakness	Persistent meningismus	Worsening after plasma exchange	Mental status changes	Improvement on IV doxycycline
CSF color	Bloody	Bloody	Bloody	Bloody	Yellow
Supernatant	—	Xanthochromic	Xanthochromic	Xanthochromic	Xanthochromic
RBC	10,000/cu mm	69,500/cu mm	85,000/cu mm	22,000/cu mm	290/cu mm
Glucose	80 mg/dl	31 mg/dl	37 mg/dl	46 mg/dl	44 mg/dl
WBC	86/cu mm (86%N)	209/cu mm (82%N)	792/cu mm (96%N)	89/cu mm (52%N)	13/cu mm (50%L)
Corrected WBC*	85/cu mm	200/cu mm	790/cu mm	86/cu mm	12/cu mm
Protein	300 mg/dl	1697 mg/dl	297 mg/dl	255 mg/dl	151 mg/dl
Corrected protein via Fishman's formula	290 mg/dl	1627 mg/dl	212 mg/dl	233 mg/dl	151 mg/dl

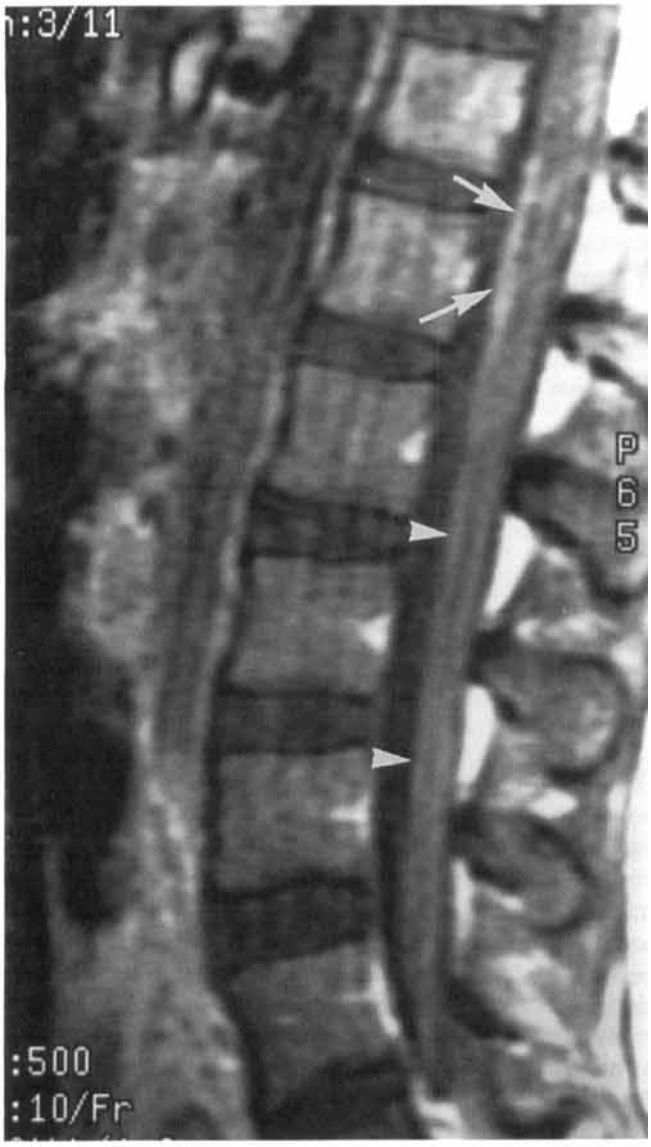
* CSF WBC Correction[10]

$$W = WBC_{CSF} - \frac{WBC_{Blood} \times RBC_{CSF}}{RBC_{Blood}}$$

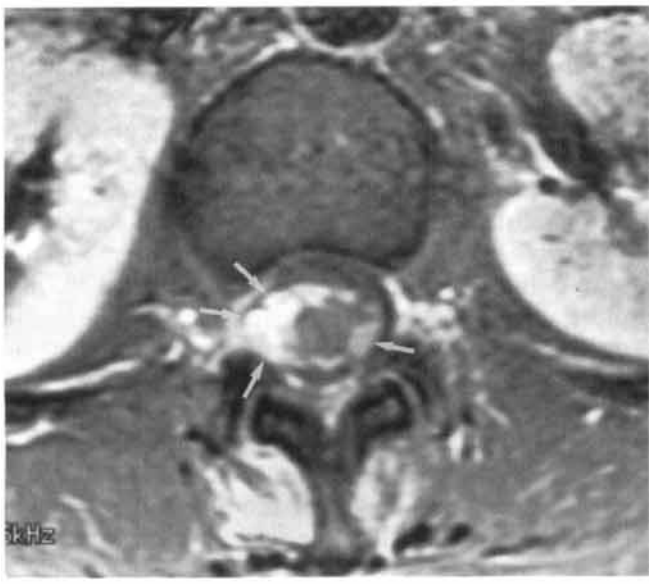
nucleolar pattern, however, complement levels and other collagen vascular disease studies were unremarkable. A T-12-L-1 intradural lesion biopsy was cancelled when CSF Lyme titers were found to be reactive at an index of 2.76 compared with a serum reactivity of 1.17 (reactive cutoff 1). This was subsequently confirmed by a second independent lab with CSF ELISA revealing 0.199 optical density (OD) (reactive cutoff 0.131 OD). The CSF Lyme Western blot analysis revealed IgG reactivity to five proteins including the immunodominant 93-kDa band. The patient was treated with doxycycline IV for 30 days with subsequent full resolution over the next 3 months. Repeat MRI 4 months following disease onset revealed partial resolution with less thickening of the cauda equina nerve roots and diminished pial surface and nerve root enhancement. Other changes were consistent with sequelae of arachnoiditis.

Discussion. The diagnosis of CNS Lyme disease in this patient is supported by the clinical presentation including meningitis, cranial neuritis and radiculitis, a history of tick bites in an endemic area, positive serology for *B burgdorferi*, and a response to antibiotic treatment. Meningitis in the second stage of Lyme disease, reflecting direct invasion of the subarachnoid space by *B burgdorferi*, is normally associated with a predominantly lymphocytic pleocytosis.[3] Our patient's CSF findings were consistent with SAH and mixed neutrophilic and lymphocytic pleocytosis. The ratio of white cells to erythrocytes and amount of protein significantly exceeded that expected with a traumatic tap. Neurosurgical criteria supported our conclusion of a spontaneous SAH within the spinal canal since the erythrocytes persistently increased during CSF drainage and a repeat tap at a higher interspace did not show clearing. Xanthochromia, which usually correlates with antecedent SAH, was present on a later lumbar puncture, but not sought on the initial examination. Other evidence supporting a spontaneous, as opposed to a traumatically induced, SAH included the extensive abnormal meningeal enhancement demonstrated on the initial spinal MRI. This imaging finding indicates the presence of an inflammatory process prior to the lumbar puncture. The enhancing nodule at T-12-L-1 contained evolving hemorrhage on follow-up MRI. It is uncertain as to whether this represented a primary hemorrhage or a blood clot adherent to the surface of this inflammatory nodule. Additionally, our patient experienced sudden recurrent SAH while undergoing plasma exchange, which likely reflected abnormal clotting factors in the setting of an active bleeding site as opposed to a traumatic spinal tap 5 days earlier. The absence of any parenchymal abnormality on spine and brain MRI, absence of abnormal flow voids to suggest abnormal vessels, and the negative cerebral arteriography ruled out the presence of ruptured aneurysm, AVM, or tumor as an alternative source of hemorrhage.

We postulate that SAH in our patient with CNS Lyme disease was secondary to vasculitis. SAH is reported in association with vasculitides including Behçet's disease,[6] Churg-Strauss syndrome,[7] and Wegener's granulomatosis[8] but has not been reported in Lyme disease. Inflammatory vasculitis is a known pathologic manifestation of Lyme disease and may be present in peripheral nerves and skin associated with both acute and remission phases of Bannwarth's syndrome (a painful meningoradiculoneuritis).[9] Blood vessel damage via an inflammatory response to the infecting spirochete or through immune complex deposition can increase vascular permeability through complement activation, neutrophil infiltration, and cytokine production. Release of intracytoplasmic enzymes such as collagenase and



A



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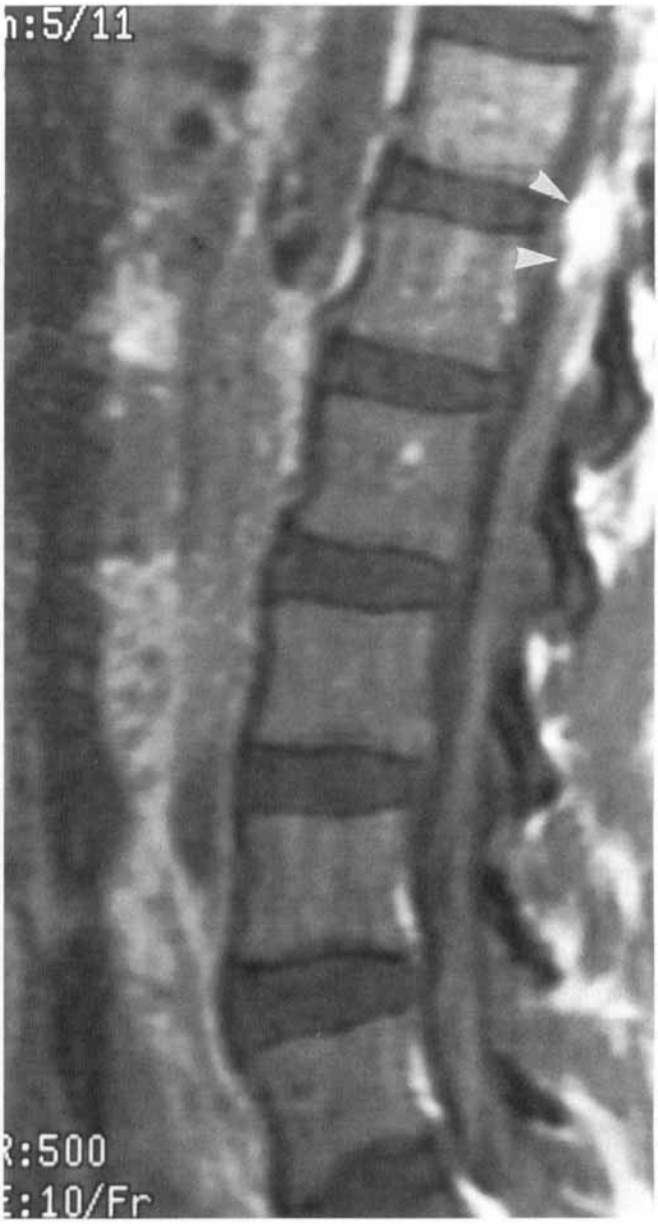

B

Figure 1. Initial MRI performed day of admission. (A) Sagittal T_1-weighted MRI of lumbar spine after gadolinium DTPA administration shows diffuse radicular/periradicular (arrowheads) and pial cord surface (arrows) enhancement. (B) Sagittal T_1-weighted MRI centered right of midline shows nodular enhancement at T-12-L-1 level (arrowheads). (C) Enhanced axial T_1-weighted MRI at T-12-L-1 level confirms thick nodular intradural enhancement more prominent on right (arrows).

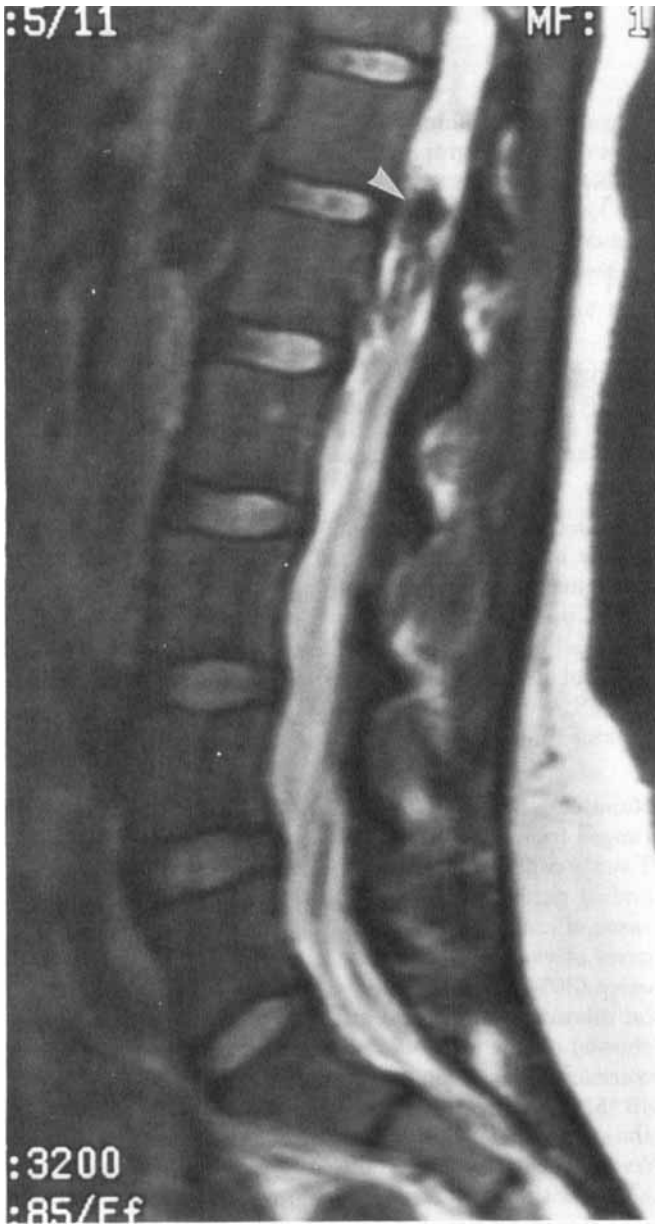

Figure 2. MRI performed 12 days after admission. Sagittal T_2-weighted MRI shows nodular hypointense focus at T-12-L-1 corresponding to enhancing nodule seen on initial examination indicating presence of subacute hemorrhage/methemoglobin (arrowhead).

elastase can contribute to endothelial cell damage causing ischemia and hemorrhage. She had hypersensitivity reactions on two different occasions that may have contributed to vascular inflammation through IgE-mediated release of vasoactive amines. The absence of an underlying structural abnormality, presence of a spontaneous SAH, and definitive diagnosis of CNS Lyme disease, both clinically and via intrathecal antibody production, suggest that vasculitis was the underlying pathology for the broad range of our patient's findings and symptoms. These included MRI evidence of arachnoiditis, SAH, meningitis, cranial neuritis, radiculitis, and possibly mild encephalopathy. The most plausible etiologies for vasculitis in our patient with CNS Lyme disease are direct spirochete invasion of the epineural blood vessels or indirect immune mechanisms such as circulating immune complexes or cross reactive autoantibodies.

Our patient manifested neurologic symptoms of meningoradiculoneuritis and mild encephalopathy associated with the chronic late-stage Lyme disease.[2,9] Since these symptoms can usually be prevented by early antibiotic treatment, it is imperative to recognize the atypical presentation of this multisystem disease, including SAH. This is particularly important in evaluating patients living in endemic areas of the northern United States, including the mid-Atlantic coastal areas.

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