Progressive Necrotic Myelopathy

Clinical Course in 9 Patients

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Objective: To review the clinical, laboratory, and radiological findings of 9 patients who had progressive idiopathic myelopathy with evidence of spinal cord necrosis.

Design and Methods: We reviewed personally examined cases of myelopathy that fulfilled the following criteria: (1) regional loss of reflexes, flaccidity, and muscle atrophy; (2) magnetic resonance imaging showing a shrunken or cavitated cord without evidence of arteriovenous malformation; (3) electromyogram showing denervation over several contiguous spinal cord segments with preservation of sensory potentials in some cases; and (4) the absence of evidence of systemic disease or neoplasm.

Results: The illness began in these patients after the age of 40 years, with prominent burning or tingling limb pain, occasionally with radicular features or with less well-defined back, neck, or abdominal pain. Leg or infrequently arm weakness appeared concurrently or soon after the onset of pain. The most distinctive feature was a saltatory progression of symptoms, punctuated by both acute and subacute worsenings approximately every 3 to 9 months, culminating in paraplegia or tetraplegia. The distinguishing clinical findings, together indicative of destruction of gray matter elements of the cord, were limb atrophy, persistent areflexia, and flaccidity. The concentration of cerebrospinal fluid protein was typically elevated between 500 g/L and 1000 g/L, without oligoclonal bands, accompanied infrequently by pleocytosis. Magnetic resonance imaging showed features suggesting cord necrosis, specifically swelling, T2-weighted hyperintensity, and gadolinium enhancement over several spinal cord segments, succeeded months later by atrophy in the same regions. Necrosis of the cord was found in biopsy material from one patient and postmortem pathology in another case, but inflammation and blood vessel abnormalities were absent. Only 2 patients had prolonged visual evoked responses. The disease progressed despite immune-modulating treatments although several patients had brief epochs of limited improvement.

Conclusions: The saltatory course, prolonged visual evoked responses in 2 patients, and a cranial abnormality on magnetic resonance imaging in another, raised the possibility of a link to multiple sclerosis. However, the normal cranial magnetic resonance imaging scans in 6 other patients, uniformly absent oligoclonal bands, and poor response to treatment were atypical for multiple sclerosis. On the basis of shared clinical and laboratory features, idiopathic progressive necrotic myelopathy is indistinguishable from a limited form of Devic disease.

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We describe a case series of patients with idiopathic progressive myelopathy and clinical and laboratory findings suggestive of spinal cord necrosis to differentiate them from typical demyelinating diseases and other spinal cord disorders. Although reports of such cases date back 100 years, it is difficult to find a concise description of the findings and clinical course in a series of patients. Necrosis in such cases is believed by many authors to be a defining property of the myelopathy of Devic disease. Nevertheless, Adams and Kubik classified neuromyelitis optica with the demyelinating diseases based on the inflammatory response and demyelination at the margins of necrotic tissue similar to typical multiple sclerosis.

We describe patients seen by us between 1981 and 1998 who had progressive idiopathic myelopathy with persistent lower motor neuron signs and evidence of spinal cord destruction confirmed by magnetic resonance imaging (MRI) or pathological study. Patients were excluded if an underlying cause for myelopathy was identified, such as trauma, arteriovenous malformation, tumor, mechanical compression, or infection, or if the illness was monophasic or of short duration.
Case 6

Patient 6: Saltatory Progression to Tetraparesis in 4 Subacute Episodes Over 2 Years in a 52-Year-Old Man. The illness began with tingling in the left forearm and shoulder that became painful, spreading to the neck and right shoulder over 2 weeks. Strength and sensation were normal, but his reflexes were increased in the legs without Babinski signs. Magnetic resonance imaging of the cervical spine showed a bulging C4–5 disk but with increased T2-signal intensity in the adjacent spinal cord. Myelography and cranial MRI were normal. The cerebrospinal fluid (CSF) had 0.002 × 10^6/L white blood cells and protein, 670 g/L without oligoclonal bands. Six months later he underwent an anterior discectomy without improvement in his condition.

Over the next 9 months he gradually had difficulty manipulating objects with his hands, intermittent leg weakness, worsening balance, and urinary frequency. The shoulders were weak, vibration sense was decreased in the fingertips and toes, and arm and leg reflexes were hyperactive with bilateral Hoffman signs, ankle clonus, and a positive Babinski sign on the left side. Magnetic resonance imaging of the cervical spine then showed cord swelling, a small area of enhancement, and cavitation in the midcervical region of the previous signal abnormality. Visual evoked potentials were normal. The left median compound muscle action potential amplitude was decreased and left median, ulnar, and radial sensory potentials were normal; fibrillations and increased motor unit action potential amplitudes and durations were present in the tested arm and in cervical paraspinous muscles.

Over the next 6 months, he had increasing difficulty walking, bladder urgency, and worsening aching neck, shoulder, and low back pain. Hand movements were slow and clumsy, there was mild right intrinsic hand muscle atrophy, and gait was spastic. As numbness worsened in his hands, it progressed from his toes to his ankles, and joint position sense was diminished acrally in all the extremities. A biopsy specimen of the enhancing cervical cord lesion showed marked gliosis. After the biopsy right hand and leg numbness and right hand clumsiness increased. Atrophy of intrinsic hand muscles advanced and right-sided weakness slowly worsened. The reflexes remained exaggerated with loss of all sensation on the right side from T3 to L1, with hyperesthesia throughout the right arm. Five months later, numbness in the left fingertips increased. He was treated intermittently with high doses of corticosteroids without improvement in his condition.

Case 9

Patient 9: Flaccid Quadriplegia Evolving Over 5 Years; Optic Neuritis and Previous Episodes Indicating Neurologic Disease in a 43-Year-Old Woman With Multiple Sclerosis (MS) and Myasthenia Gravis. The illness began with tingling in the feet which spread to the lower legs over 2 days. Five months later she awoke with severe interscapular pain, intense tingling, and numbness in her legs and right trunk up to her breasts, imbalance, and urinary urgency. The arm and leg reflexes were brisk with a right Babinski sign. There was a subtle midthoracic sensory level that was slightly higher on the right side, and vibration sense was decreased in the legs. Magnetic resonance imaging showed T2-weighted hyperintensity and enhancement at T3 to T5. She was treated with oral prednisone, 60 mg/d, that was slowly tapered over 9 months. Ten months later severe aching intrascapular pain appeared and over 8 days she acquired a flaccid paraplegia with retained reflexes and positive Babinski signs. Sensation was absent below the level of T5. The CSF had 500 × 10^6/L white blood cells (with 0.81 neutrophils and 0.17 lymphocytes) and a protein concentration of 2310 g/L without oligoclonal bands. Magnetic resonance imaging of the cervical and thoracic spine showed increased T2-weighted signal in the central cord from C2 to T11 with patchy leptomeningeal enhancement. Serum antinuclear antibodies, angiotensin-converting enzyme, Lyme antibody titer, human immunodeficiency virus titer, and anticardiolipin antibody levels were normal. Cerebrospinal fluid viral cultures, specifically including those for herpes simplex virus and human T-cell lymphotrophic virus type 1 were negative, and brainstem auditory evoked responses and visual evoked responses were normal. A biopsy of the midthoracic cord showed softened, gray, and necrotic tissue. There was demyelination, relative preservation of the axons, and infiltration with macrophages and lymphocytes. She was treated with intravenous (IV) cyclophosphamide, 1.7 g/d for 1 day only, and 6 days of IV methylprednisolone sodium succinate, 250 mg/d, that was then slowly tapered.

Seventeen months after the first symptoms, she had painful visual loss in the left eye accompanied by numbness over the left biceps and hyperesthesia of the left C5 dermatome. The CSF had 0.01 × 10^6/L white blood cells and the concentration of protein was 980 g/L without oligoclonal bands. Over 8 months her leg strength improved and she was able to assist with transferring to and from her wheelchair.

Thirty-three months after the first symptoms, flaccid areflexic tetraplegia ensued over several days, followed by blindness of the right eye, right lower facial palsy, and loss of sensation below the T-2 dermatome. Treatment with cyclophosphamide, 1200 mg/d, and IV methylprednisolone sodium succinate, 1 g/d, for 5 days were unassociated with improvement in her condition. Six months later respiratory distress and a bandlike sensation across the chest occurred. Magnetic resonance imaging showed T2-weighted hyperintensity of the entire cervical cord with T1-weighted hypointensity at C3, and severe atrophy from C7 to T1 (Figure 1). She was treated with IV methylprednisolone followed by a tapering dosage of oral prednisone and 9 monthly IV cyclophosphamide treatments, after which the right arm could be raised to shoulder level and wrist extension strength was 4/5. The muscles of the right hand were greatly atrophied and the legs were flaccid and paralyzed.
RESULTS

COURSE AND CLINICAL FINDINGS

Several features were noteworthy because they were virtually uniform in our 9 patients (Table) and were distinct from those of typical MS. All had the onset of illness after the age of 40 years, the average age being 59 years. The first symptoms were pain and leg weakness, or in a few instances arm weakness, coupled with urinary incontinence; these often appeared on awakening. Three patients had an abrupt onset of the myelopathy, and then paraplegia or tetraplegia culminating within weeks. In the other 6 patients the early illness advanced more indolently with a gradual progression of weakness and urinary incontinence. The most characteristic feature occurring in 8 of 9 cases, and not previously emphasized, was a saltatory course that was punctuated by acute and subacute worsenings approximately every 3 to 9 months. Deficits accrued by these cumulative episodes, remitting to any significant extent in only a few instances, as exemplified by patient 8 (Figure 2); leg weakness progressed at first insidiously and, after 9 months of quiescence, suddenly worsened, followed by 7 months of slow progression, then another discrete and rapid decline, 3 months of quiescence, and finally 6 months of slow advancement. Only in patient 4 did the temporal pattern and clinical features stand apart by virtue of a more acute course seemingly preceded by a viral infection, thereby implicating postinfectious encephalomyelitis.

Pain was prominent in 7 patients representing the initial symptom in 5 patients, and was the sole manifestation for several days in 1 patient. Discomfort was most often in the limbs, described as burning or tingling, occasionally with radicular features, eg, pain in the scapular region radiating through the lateral arm and the fourth and fifth digits. Pain in the back, neck, or abdomen was less well defined taking the forms of bandlike tightness, burning over or between the shoulder blades, aching, and a fistlike sensation in the right upper quadrant. Hyperesthesias and dysesthesias occurred in 5 cases.

Besides the saltatory progression and pain, other distinctive clinical features were atrophy, areflexia, and limb flaccidity in the absence of a state of spinal shock. These signs were present in 8 of 9 patients and were corroborated by electromyogram as discussed later. The additional early symptoms were equally distributed between sensory and motor complaints: specifically, paresthesias, heaviness or numbness, and weakness. Urinary incontinence occurred within 4 weeks of the onset of illness in 6 patients and was among the initial symptoms in 2 patients. A sensory level ascended and ultimately became established in the upper thoracic region, generally between T3 and T5.

Figure 1. T2-weighted sagittal cervical and thoracic magnetic resonance imaging scans showing centrally increased signal and severe atrophy of lower cervical and upper thoracic cord in patient 9 (A), central cavitation of the thoracic cord in patient 5 (B), and large regions of increased T2-weighted signal and expansion of the spinal cord in patient 7 (C).
MRI FINDINGS IN THE SPINAL CORD

There were abnormalities in all 8 patients studied with spinal MRI scans. Magnetic resonance imaging in the first weeks of illness showed widespread abnormalities of the cord consisting of a centrally placed spindle- or tubular-shaped hyperintensity on T2-weighted sequences and swelling that generally encompassed multiple contiguous segments of the spinal cord (Figure 1), rarely with scattered regions of hyperintensity on T1-weighted MRIs that probably represented small areas of hemorrhage. In 4 patients virtually the entire length of the spinal cord showed signal abnormalities. In 3 patients only the cervical cord was involved, and in 1 patient the changes were limited to a single thoracic segment. Weeks or months later, severe atrophy or cavitation of the cord supervened in the same regions where swelling and T2-weighted signal change was detected (Figure 1 and Figure 3).

CSF FORMULA, VISUAL EVOKED POTENTIALS, AND CRANIAL MRI

Oligoclonal bands were not detected in the CSF. Eight patients had moderate elevations of CSF protein concentration, usually in the range of 500 to 1100 g/L, and in patient 9 it was extremely high (2310 g/L) but later returned to normal. Three patients had CSF pleocytosis between 0.010 and 0.05 ×10^9/L white blood cells, often normalizing when retested weeks later. We have not generally used IgG levels or synthesis rates on our neurology service and cannot comment on them.

One patient eventually developed optic neuritis after 17 and 33 months, and 2 others had mildly and symmetrically prolonged evoked potentials without symptoms. Visual evoked responses were normal in 2 other patients. Cranial MRI showed periventricular white matter lesions, possibly suggestive of MS, in only 1 of 7 patients. The patient with presumed acute disseminating encephalomyelitis did not undergo cranial MRI but necropsy showed only 2 small demyelinative lesions, as detailed in “Pathological Features” subsection below.

ELECTROMYOGRAM

In 5 of 6 patients a motor neuronopathy was corroborated by demonstrating denervation in the myotomes of cord segments showing MRI signal change. In denervated regions there were reduced compound muscle action potentials but preserved sensory potentials. Fibrillations were numerous over several contiguous segments including in paraspinal muscles, but fasciculations were never prominent, in keeping with their absence clinically.
Cervical cord biopsy specimens were obtained from areas of suspected necrosis or enhancement from patients 6, 8, and 9 after 24 months, 13 months, and 18 months of illness, respectively. In patient 6 there was marked gliosis without inflammation; in patient 8 reactive lymphocytes were seen without a perivascular distribution; and in patient 9 there was necrosis with disrupted tissue architecture and minimal reactive lymphocytes. In patient 4, autopsy showed coagulative necrosis over virtually the entire longitudinal extent of the cord. The destroyed tis-

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<tr>
<th>LMN Signs</th>
<th>MRI Scan Findings</th>
<th>Pathological Features</th>
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<tr>
<td>Hand atrophy and areflexia</td>
<td>Cervical and thoracic swelling and extensive patchy T2-weighted hyperintensity without enhancement</td>
<td>. . .</td>
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<tr>
<td>None</td>
<td>Cervical cord swelling, T2-weighted hyperintensity, ovoid signal hypointensity, and enhancement at T6</td>
<td>. . .</td>
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<tr>
<td>Areflexia</td>
<td>Swelling of thoracic cord with T2-weighted hyperintensity and enhancement followed in 4 mo by atrophy. Low T1 signal in the cervical cord and medulla</td>
<td>. . .</td>
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<tr>
<td>Hand and leg atrophy and areflexia denervation on EMG</td>
<td>Not done</td>
<td>Necropsy showed longitudinal necrosis, vascular proliferation</td>
</tr>
<tr>
<td>Calf atrophy and areflexia denervation on EMG</td>
<td>Severe atrophy, T2-weighted hyperintensity of thoracic cord, and swelling at T12</td>
<td>. . .</td>
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<tr>
<td>Hand atrophy denervation on EMG</td>
<td>Increased signal at C4 followed by swelling, enhancement, and microcavitation</td>
<td>Biopsy showed gliosis</td>
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<td>Decreased CMAPs</td>
<td>Normal, then C1-C7 T2-weighted hyperintensity, swelling, central hypointensity at C3, diffuse enhancement, and Dawson fingers on cranial MRI scan</td>
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<tr>
<td>Calf and foot atrophy areflexia denervation on EMG</td>
<td>C4-7 swelling and T1-weighted hypointensity with enhancement, followed in 3 mo by severe cervical cord atrophy</td>
<td>Biopsy showed reactive lymphocytes</td>
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<tr>
<td>Hand atrophy areflexia</td>
<td>Thoracic T2-weighted hyperintensity, enhancement, then atrophy, cervical hypointensity, swelling, and severe atrophy</td>
<td>Biopsy showed demyelination and necrosis</td>
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Figure 3. Patient 5. A, T2-weighted thoracic axial image showing central cavitation. B, Cervical axial image showing severe atrophy and centrally increased signal intensity.

PATHOLOGICAL FEATURES

Cervical cord biopsy specimens were obtained from areas of suspected necrosis or enhancement from patients 6, 8, and 9 after 24 months, 13 months, and 18 months of illness, respectively. In patient 6 there was marked gliosis without inflammation; in patient 8 reactive lymphocytes were seen without a perivascular distribution; and in patient 9 there was necrosis with disrupted tissue architecture and minimal reactive lymphocytes. In patient 4, autopsy showed coagulative necrosis over virtually the entire longitudinal extent of the cord. The destroyed tis-
Sue retained the consistency of a soft ribbon below C4–C5 with several areas of incompletely preserved cervical cord that were buckled (Figure 4). The cut surface in the upper cervical region showed necrotic material centered at the junction of the dorsal columns and the central gray matter. The microscopic findings at C5 showed an oval area of necrosis in the ventral-most part of the dorsal columns (Figure 5, A) with many macrophages and few reactive astrocytes. The central gray matter was vacuolated and neurons in the posterior horns were pyknotic. The surrounding dorsal columns were completely demyelinated and gliotic. The necrotic area expanded in a centripetal fashion as it descended through the cervical cord, encompassing it completely at C7 (Figure 5, B). Thoracic and lumbar segments showed coagulative necrosis with no recognizable architecture, and in the conus there was marked pial thickening and necrosis, large numbers of lymphocytes, macrophages, and some vascular proliferation, but with otherwise normal vessels. The anterior roots were demyelinated and thinned, in contrast with the normal posterior roots. There were very small areas of demyelination in the right calcarine cortex and left superior cerebellar peduncle with reactive gliosis but without inflammation. The optic nerves were normal.

**RESPONSE TO TREATMENT**

Patients were treated with one or another corticosteroid, generally in high doses, as well as variously with cyclophosphamide, plasma exchanges, and in 1 case lomustine because of an erroneous diagnosis of oligodendroglioma. In all patients the illness ultimately progressed despite aggressive care. Temporary remissions or minor improvements in the patients’ conditions were not clearly related to treatment. In 3 cases, acute worsenings within the first year were followed by a significant but short-lived return of leg strength, going from bed bound to ambulatory for up to 1 year, before again losing ground.

**COMMENT**

It is difficult to be confident of the diagnosis of progressive necrotic myelopathy (PNM) in the absence of pathological examination unless a patient is observed for a considerable period, because clinical and laboratory tests generally lack specificity for cord necrosis. However, reasonable certainty in the diagnosis can be achieved when patients with an asymmetric myelopathy exhibit the particular clinical, CSF, MRI, and EMG findings detailed earlier.

The most distinctive clinical findings in our patients were (1) a saltatory progression seen in all patients followed up for 1 year or longer (Figure 2), (2) prominent pain early in the course of illness, and (3) lower motor neu-
rion signs consisting of atrophy, areflexia, and limb flaccidity in the absence of the state of spinal shock. Destruction of gray matter structures over several segments of the cord was corroborated by EMG and by serial spinal MRI showing swelling followed by cavitation or atrophy. Mirich et al2a identified this MRI pattern as indicative of necrotic myelopathy. The early imaging findings in PNM are similar to those of postinfectious myelitis or expansion of the cord due to an intramedullary tumor; atrophy is also seen with infarctive cavitation from any cause including vascular malformations. However, swelling, T2-weighted hyperintensity over multiple segments, and T1-weighted hypointensity, followed by atrophy or cavitation in the identical region more likely denote a necrotic myelopathy. All of these findings occurred in the context of elevated CSF protein concentrations without oligoclonal bands, thus differentiating these cases from typical MS.

While comprehensive autopsy pathological features were available only from patient 4, the findings were similar to those described by Hoffman,3 namely, noninflammatory necrosis with normal vessels. Foix and Alajouanine refer to small arteries being narrowed by “mesoendovascularitis.” Greenfield and Turner4 elaborated on similar abnormal intramedullary vessels that most likely reflected a genuine arteriovenous malformation or a response to necrosis rather than a unique and causative abnormality. Previous literature perpetuates the notion that microvascular changes represent a distinct entity, and confuses the vascular response to necrosis with arteriovenous malformations. With reference to such cases, Follis and Netsky5 cautioned that the term “Foix-Alajouanine disease” should not be considered a diagnosis as it has been adopted to describe a variety of unrelated vascular conditions.

An ischemic basis for tissue destruction in patient 4 was tentatively supported by the spindle-shaped area of necrosis that was demarcated from the surrounding damaged upper cervical cord (Figure 5, A). This configuration has been linked to an ischemic mechanism, as it is seen after profound systemic hypotension and occasionally after extramedullary cord compression.6

Little useful diagnostic or causative information was gained from biopsy specimens of the cord and we would not undertake this procedure again unless radiological findings of cord swelling with enhancement and a subacute progression made the prospect of an intramedullary neoplasm or granulomatous disease likely.

Neurologists are familiar with a necrotic myelopathy similar to PNM in Devic disease and there is no cogent way to separate the two. The 8 patients with Devic disease studied by Mandler et al7 were similar in many respects to our patients, with the obvious exception of optic neuritis. The essential point is the uncertainty of the later development of optic neuritis or other signs of MS if follow-up had been extended in our patients although in the 12 patients with Devic disease described by O’Riordan et al,8 almost all developed optic neuropathy within 2 years. Only 1 of our patients acquired optic neuritis and could be construed as having the pattern of Devic disease. The remaining 8, followed up from 8 to 30 months (average follow-up, 19 months), had no such symptoms. Unresolved is the issue of classifying cases of PNM with abnormal visual evoked responses but lacking the clinical manifestations of optic neuritis, as seen in 2 of our patients.

The saltatory progression in our patients suggests a connection between PNM and MS, but prominent pain, lower motor neuron signs, minimal remissions, and recalcitrance to treatment would be atypical of MS. Furthermore, normal cranial MRI and the absence of oligoclonal bands did not support a connection between PNM and MS in most cases. The long-lived controversy surrounding the relation between Devic disease and MS cannot be resolved, and the ambiguity holds equally for that between PNM and Devic disease. Perhaps Devic disease and MS are related in a fashion similar to axonal and demyelinating Guillain-Barré syndrome, the former showing damage to the neuronal processes, a lack of inflammation, and poor response to treatment, in contrast with the more common inflammatory-demyelinating neuritis that has a better prognosis. In a similar fashion there may be separable axonal and demyelinating immune diseases of the spinal cord. This agrees with common experience and the suggestion of Lipon and Teasdalea that necrosis in the spinal cord is a reaction that may be common to several processes, one of which is an immune attack.

While the etiology of PNM is unclear, its detailed description should be useful for clinical work and its identification as an entity allows for more precise studies to determine the cause. After excluding arteriovenous malformations, paraneoplastic, infectious, compressive, and infarctive causes, a myelopathy beginning in middle-aged patients with subacute and saltatory progression, pain, a combination of upper and lower motor neuron findings, absence of optic neuritis, moderate elevation of CSF protein concentration but without oligoclonal bands, characteristic MRI appearance, and relative resistance to treatment, is likely to be PNM of the variety we describe.

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