Vasculitis of the Spinal Cord

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Background: Vasculitis of the central nervous system is rare but well described. It affects the cerebral hemispheres predominantly and only exceptionally involves the spinal cord.

Objective: To describe a case of spinal cord vasculitis with unusual pathologic changes.

Design: Case report with clinicopathologic correlation.

Case Description: A young man developed leg weakness and sensory symptoms over several weeks. He had an asymmetric paraparesis with impaired vibration sense in the feet and a Romberg sign but no sensory level. The cerebrospinal fluid contained 123 white blood cells × 10³/µL, mostly lymphocytes, and a protein concentration of 52 mg/dL; oligoclonal bands were not detected, but the illness simulated multiple sclerosis. Magnetic resonance imaging scans of the spinal cord and brain were normal. His condition improved on several occasions with intravenous infusions of corticosteroid agents, but his neurologic signs gradually worsened over several months, and he acquired a thoracic sensory level and sphincteric abnormalities. An explosive preterminal illness occurred with paraplegia, nystagmus, and coma. The findings of a pathologic examination showed numerous ischemic areas in the spinal cord, some cavitated, and a vasculitis of the leptomeningeal branches of the anterior spinal artery and of subpial vessels. The vessel walls were not necrotic, but many of their lumens were occluded by fibrinous material. There were similar findings in regions of cerebral hemorrhagic infarction.

Conclusions: A destructive and vasculitic process should be considered in cases of subacute myelopathy with persistent cellular reaction in the cerebrospinal fluid and clinical responsiveness to corticosteroid therapy. The magnetic resonance imaging scan of the spinal cord may be normal.

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A N IDIOPATHIC variety of cerebral vasculitis unassociated with systemic disease is well known. Rare cases have been linked with certain nonvasculitic diseases, such as Hodgkin lymphoma and Hashimoto thyroiditis, and with drug-induced allergic reactions. The cerebral pathologic status in these cases has been variously described as a perivascular inflammation, widespread vascular occlusion, or in its most severe presentation, inflammatory destruction of vessel walls with microvascular occlusion.

We report a case of vasculitis that is notable because it was initially limited to the spinal cord and simulated multiple sclerosis. A terminal phase included hemorrhagic infarction at several sites in the brain. In addition to an initially isolated myelopathy, the unusual features were a persistent inflammatory reaction in the cerebrospinal fluid (CSF) and occlusion by fibrinoid material of many leptomeningeal vessels of the cord.

REPORT OF A CASE

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in the toes and a Romberg sign; there was no sensory level. The CSF had 123 white blood cells × 10^3/µL, 98% lymphocytes, a protein concentration of 52 mg/dL, and a normal glucose level. Oligoclonal bands or myelin basic protein were not detected but the IgG concentration was elevated at 8.1 mg/dL. There were no abnormalities seen on magnetic resonance imaging scanning of the brain, and cervical, thoracic, and lumbar spine, all performed with and without gadolinium 64 contrast enhancement. Results of routine laboratory studies including erythrocyte sedimentation rate were likewise normal.

He was thought to have multiple sclerosis and was treated with intravenous methylprednisolone, 500 mg/d, for 5 days. His numbness and leg strength improved markedly over 2 weeks but then worsened gradually over several weeks as he became wheelchair bound. Over the subsequent weeks he acquired paresthesias of the fingertip and numbness below a perceived level in the upper thorax. There was no difficulty with mentation, cranial nerves, or arm function. He was unable to lift his legs off the wheelchair pedals and a pinprick sensory level was detected at T8 on the right side and T6 on the left side. The deep tendon reflexes were increased (3+) in the upper extremities and markedly increased (4+) in the lower extremities with bilateral Babinski signs. The CSF, 1 month after the first symptoms, contained 88 white blood cells × 10^3/µL, 98% polymorphonuclear cells, and a protein concentration of 325 mg/dL. Intravenous methylprednisolone, 500 mg/d, was administered for the third time. Respiratory failure developed over several hours; he became persistently lethargic. He was afebrile but had no signs of systemic disease except for an enterococcal urinary tract infection and peripheral white blood cell count of 11.7 × 10^3/µL with 94% polymorphonuclear cells.

Left beating nystagmus was detected; the sensory level for pinprick had ascended to T3. Further serum and CSF study results were unrevealing. Magnetic resonance imaging scans demonstrated extensive increase in T2-weighted signal intensity of the pons and upper medulla. The abnormal signal extended to the upper cervical cord and into the midbrain, inferior and middle cerebellar peduncles, both cerebral peduncles, and inferior basal ganglia, more on the right side than on the left side. Most of the lesions showed patchy enhancement with gadolinium 64. There were also small indistinct areas of increased T2-weighted signal within the cord at the C1-2 and T2-T3 levels and within the conus. Imaging of the cerebral hemispheres was normal. Results of numerous serologic and bacteriologic studies from the serum and CSF samples were normal including the following: VDRL, cytomegalovirus, varicella-zoster virus, herpes simplex virus types 1 and 2, human immunodeficiency virus, Lyme disease, antineutrophil cytoplasmic antibody, antinuclear antibody, and oligoclonal bands.

He was again treated with doses of methylprednisolone sodium succinate (Solu-Medrol), as well as ganciclovir, and ampicillin. He became comatose and his respiratory effort declined over 24 hours. His pupils were normal, but eye movements could not be induced and the corneal reflexes were absent; he later developed ocular bobbing. There were no spontaneous or pain-induced movements except for triple flexion of his legs. Plasma exchanges were instituted and cyclophosphamide therapy was administered. The electroencephalogram showed generalized slowing. After 3 days his right pupil became fixed and dilated, gradually followed by the left pupil. His systolic blood pressure dropped below 90 mm Hg; he died 15 days after the onset of the acute decline and 5 months after the onset of the first neurologic symptoms.

PATHOLOGIC EXAMINATION FINDINGS

Only the brain and spinal cord were examined. The ventral surface of the brainstem was hemorrhagic, with an exophytic clot emerging from the pons into the subarachnoid space. The brainstem was swollen, and the cerebellar tonsils were bilaterally prominent, but they did not compress the medulla. Transverse sections of the brainstem revealed extensive hemorrhage and necrosis with a solid blood clot in the midpons. Scattered brainstem hemorrhages extended from the medulla up to the rostral midbrain, hypothalamus, and subthalamic regions bilaterally, with the greatest amount of blood in the pons. Hemorrhage extended laterally into the middle cerebellar peduncles, with small zones of hemorrhage present in the cerebellum.

Regarding the cord, there were numerous small areas of cavitation, some with hemosiderin-laden macrophages in their margins (Figure 1). Rarefaction was seen in the subpial zones and foci of myelomalacia in other areas. The thoracic cord had patchy zones of pallor in

Figure 1. Cavitary infarction in the lower thoracic cord. Some blood breakdown products are seen in macrophages at the upper margins of the lesion (hematoxylin-eosin, original magnification ×20).
the posterior columns but no hemorrhagic lesions. The posterior columns were pale in the myelin stains. The spinal leptomeninges were slightly thickened and fibrotic, without granuloma formation. Numerous arteries, and to a lesser extent veins, in the spinal leptomeninges were surrounded and infiltrated by normal-appearing lymphocytes, and rare polymorphonuclear cells but no eosinophils, plasma cells, or histiocytes. The most striking inflammatory response was found in relation to branches of the anterior spinal artery where numerous leptomeningeal vessels at all levels were affected (Figure 2). In one section the inflammation extended into the substance of the spinal cord around branches of the anterior spinal artery, but otherwise the inflammation was limited to the vessels in the meninges. Several leptomeningeal vessels were inflamed and occluded (Figure 3). In addition, many of the smaller vessels in the subpial region were occluded with fibrinous material but showed no inflammation. A few arteries had thickened walls and subintimal eccentric proliferation of fibrous tissue, but few were hyalinized. Endothelial swelling and disruption was frequent; however, necrosis of vessel walls was rare. The infiltrate was composed of CD3 cells but did not contain CD4 or CD20 cells. A small proportion were CD8 positive.

In the cerebrum, there were foci of fibrinoid necrosis of arterial walls and numerous smaller vessels with fibrin occlusions. Mild inflammatory leptomeningeal vascular changes were seen in the region of the hippocampus, temporal lobe, hypothalamus, pons, cerebellum, and spinal cord. The subpial vessels did not demonstrate these inflammatory changes. Recent petechial hemorrhages were observed in the brainstem, cerebellar white matter, hypothalamus, and subthalamus as well as the aforementioned larger clots. In and around the zones of hemorrhage, there was neuronal loss, perhaps indicating ischemia that may have preceded the bleeding. The appearance was overall suggestive of hemorrhagic infarction. The frontal and occipital lobes, basal ganglia, cerebellar vermis, and pituitary gland were normal. There were neither zones of demyelination nor dysplastic vessels or arteriovenous malformation at any level.

COMMENT

This case of subacutely progressive myelopathy is of interest because of a persistently inflammatory CSF formula, a degree of responsiveness to corticosteroid therapy, and an explosive terminal phase that caused necrotic and hemorrhagic lesions; there was notable absence of magnetic resonance imaging signal change until the process was fully developed. This young man had an aggressive and isolated central nervous system vasculitis that involved predominantly the leptomeningeal arteries of the spinal cord and considerably later, the brainstem and diencephalon. The process was initially considered a myelitis, possibly related to multiple sclerosis, for which no causative factors such as infectious agents, systemic vasculitis, or malignancy could be identified, despite extensive evaluation.

A somewhat similar case of apparently isolated spinal cord arteritis, fatal in 6 months, was described by Feasby et al.1 There was patchy necrosis and demyelination involving the entire cervical spinal cord, as well as acute and chronic inflammatory changes of a necrotizing vasculitis. The intramedullary vessels were mostly affected, including moderate necrosis of vessel walls. In our patient the intramedullary vessels were largely spared, and, in addition to mild vasculitis of arterioles, there was some inflammatory activity in and around veins; the lesions were also much more widespread, involving the entire spinal cord and brainstem, eventually with a prominent hemorrhagic component. The parenchymal lesions in the spinal cord and brainstem in our patient were consistent with infarction, which we presume was as a result of vasculitic ischemia.

Alternative processes such as intravascular lymphoma and systemic vasculitides were excluded by the pathologic examination, but some features were shared with certain reported cases of systemic lupus erythematosus and with a singular case of cryoglobulinemia.2 One aspect of the latter cases that were similar to our case was the occlusion of numerous small vessels with fibrinoid material, but an inflammatory response was lacking. A lymphocytic infiltration of leptomeningeal veins and ven-
ules, sparing the parenchymal vessels, and limited to the brainstem, has also been reported in a patient with Hashimoto encephalopathy, but the connection between these entities is obscure.

Although not in accord with our experience, spinal cord involvement has been emphasized in many patients with Sjögren syndrome, most often in the form of acute or subacute transverse myelopathy. In the series by Alexander et al., 3 of 16 patients with Sjögren syndrome had myelopathy, 2 had an isolated chronic progressive syndrome, and the third had spinal subarachnoid hemorrhage from necrotizing anterior spinal arteritis. A necrotizing vasculitis that led to subarachnoid hemorrhage was found by de la Monte et al. in another case of Sjögren syndrome. Our patient had no systemic features suggestive of Sjögren syndrome or other vasculitis and the results of extensive serologic studies were negative, but assays for Sjögren-associated antibodies were not performed and a biopsy specimen of the lip was not obtained.

Central nervous system vasculitis in connection with viral infection (mainly cytomegalovirus, varicella-zoster virus, and human immunodeficiency virus) seems an unlikely explanation in our patient; there were no inclusion bodies, and CSF serologic studies and varicella-zoster virus and herpes simplex virus immunohistochemistry results were negative for organisms.

Our case also differs from the rare small vessel granulomatous vasculitis of the central nervous system that has occurred in association with lymphoma. For example, an intense arteritis and necrotizing myelopathy of spinal cord involvement has been reported in a patient with Hodgkin lymphoma. Most inflammatory cells were granulocytes and histiocytes, with only a few lymphocytes. Several exceptional cases related to lymphoma had spinal cord involvement, similar in some ways to our patient; however, the predominant involvement of extra-medullary vessels in our patient and lack of histiocytic infiltration, multinucleated giant cells, or granuloma formation differ. Furthermore, there was no evidence of an underlying systemic disease such as lymphoma or human immunodeficiency virus. Also in contrast to the case we report herein, the predominant cell type in idiopathic granulomatous vasculitis of the central nervous system has been the CD4+ T lymphocyte. The inflammatory infiltrate in our patient was predominantly lymphocytic, and most cells were CD4+/CD8−/CD3+ T cells. This antigenic configuration is probably consistent with immature T lymphocytes, since natural killer cells do not express CD3 molecules.

This case of inflammatory and partly destructive myelopathy was predicated on a leptomeningeal vasculitis. Fibrinoid occlusion of many vessels was a peculiar feature. A condition such as this should be considered when there is a persistent meningeval inflammatory reaction, corticosteroid-related improvement in clinical features, and a normal magnetic resonance imaging scan.

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REFERENCES