Case Report

Central Nervous System Vasculitis as a Complication of Refractory Dermatomyositis

MICHAEL REGAN, UZMA HAQUE, MARTIN POMPER, CARLOS PARDO, and JOHN STONE

ABSTRACT. We describe a 47-year-old woman with refractory dermatomyositis (DM) who developed progressive cognitive dysfunction. Magnetic resonance imaging showed a large cerebral infarction, and the diagnosis of central nervous system (CNS) vasculitis was confirmed by both angiogram and brain biopsy. Her DM and CNS vasculitis responded promptly to the institution of daily cyclophosphamide, and her previously refractory disease entered remission. (J Rheumatol 2001;28:207–11)

Key Indexing Terms:
DERMATOMYOSITIS CENTRAL NERVOUS SYSTEM VASCULITIS

Dermatomyositis (DM) is a form of inflammatory myopathy in which the immune system targets the microvasculature of skeletal muscles and skin, leading to an obliterative vasculopathy mediated by complement[1,2]. We describe a patient who developed central nervous system (CNS) vasculitis in the setting of refractory DM. The occurrence of vasculitis has been reported in organs other than the skin and muscles in DM, but to our knowledge, the occurrence of CNS vasculitis has never been described in an adult patient.

CASE REPORT

In March 1996, a 47-year-old Caucasian woman developed facial erythema in a malar distribution. Over the next few weeks, the rash extended to involve her nasal bridge, forehead, and eyelids. Her rash improved with prednisone treatment, but repeatedly flared when tapers were attempted. In March 1997, one year after onset of the rash, she developed proximal muscle weakness and was admitted to a local hospital, where her creatine kinase (CK) level was 797 mg/dl (normal 0–150 mg/dl). Biopsy of the right deltoid muscle revealed a perivascular lymphocytic infiltrate and perifascicular atrophy, diagnostic of DM. By April 1997, despite treatment with high doses of prednisone, she had become progressively weaker and developed dysphagia, and she was transferred to our center.

On transfer, she had profound proximal muscle weakness and was unable to perform activities of daily living. She denied fevers, night sweats, oral or nasal ulcers, arthralgias, pleurisy, and Raynaud's phenomenon. Her medications included prednisone 60 mg/day and metoprolol 50 mg/day. Examination of her skin revealed a heliotrope rash; Gottron's papules over her MCP, PIP, knee, and elbow joints; pronounced dilatation of the nailbed capillaries; and diffuse erythema of her face, hands, and "shawl" region. She had 3/5 strength in her proximal muscle groups and 4/5 strength distally. Her CK was 5000 mg/dl (normal 0-150 mg/dl), and the erythrocyte sedimentation rate (ESR) was 30 mm/h. An antinuclear antibody screen was positive at a titer of 1:2560 with a fine, speckled pattern. Assays for antibodies to double-stranded DNA, Ro, La, Sm, and RNP were negative.

She was treated with methylprednisolone (1 g/day for 3 days), and methotrexate (MTX) 7.5 mg po/week was added to her regimen. Weakness of the soft palate and superior pharyngeal muscles, confirmed by cine-esophagram, resulted in continued nasopharyngeal regurgitation. A percutaneous endoscopic gastrostomy (PEG) tube was placed because of recurrent aspiration. Investigations for malignancy, including mammography, flexible sigmoidoscopy, and pelvic ultrasonography, were unrevealing.

She was discharged taking prednisone 80 mg/day and MTX 7.5 mg/week. Over the ensuing weeks, her muscle strength improved and her CK normalized as her MTX dose was increased and her prednisone tapered. During the first year after starting MTX, however, several flares of DM, manifested by worsening proximal muscle weakness and tenderness in her periungual regions, required brief increases in her prednisone dose, followed by resumptions of her taper. By June 1998, 14 months after the start of treatment with MTX, the dose was 22.5 mg/week, and her prednisone had been tapered to 10 mg/day. She had resumed her normal activities, and the PEG was removed. However, her skin disease remained active. Despite the addition of hydroxychloroquine (HCQ) 400 po mg/day, her cutaneous DM remained active, with persistence of the diffuse, scaly erythema; intense scalp pruritus; Gottron's papules; and dilated nailbed capillary loops.

In July 1998, she noted the onset of subtle cognitive dysfunction. She suffered progressive short term memory impairment, organizational difficulties, and episodes of confusion. She was discovered searching aimlessly through a closet in the middle of the night. Two days later, she suffered a tonic-clonic seizure and was taken to a local emergency room. A computed tomography scan of the brain revealed a low attenuation lesion in the white matter of the right frontal lobe.

On examination, her vital signs were normal, but she had a cushingoid facies and persistent signs of cutaneous DM. The neurological examination revealed no focal deficits apart from 4/5 strength in both proximal and distal muscle groups. A complete blood count, serum electrolytes, and chemistries (including muscle enzyme levels) were normal, but her ESR was 51 mm/h. A lumbar puncture revealed an increased protein concentration in the cerebrospinal fluid (CSF) (74 mg/dl, normal 15–45 mg/dl), but a normal CSF glu-

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cose and only 2 white blood cells/mm^3. The CSF cytology was negative for malignant cells, and cultures for microbial pathogens (bacteria, viruses, and fungi) and a CSF VDRL test were all negative. A magnetic resonance imaging (MRI) study of the brain showed increased T2 signal in the frontal lobes with corresponding enhancement (Figure 1). The differential diagnosis of this lesion is discussed below.

She underwent cerebral angiography, which showed segmental narrowing in 2 distributions of the right internal carotid artery, consistent with vasculitis (Figure 2). A stereotactic brain biopsy of the right frontal lobe revealed infiltration of small blood vessels by inflammatory cells (Figures 3A, 3B). Marked astrogliosis and a pronounced microglial/macrophage reaction were present. Stains for microbial and fungal pathogens and immunocytochemical studies for papovavirus were negative. Additional immunocytochemical studies disclosed that the cellular infiltrate around and within blood vessel walls was principally made up of T cells and some plasma cells (Figure 3C). B cell and proliferation markers were negative in the cells infiltrating the blood vessels, excluding the possibility of lymphoma. Cultures for bacteria, fungi, mycobacteria, and atypical organisms, as well as a polymerase chain reaction (PCR) assay for JC virus, were all negative. In the absence of an infection, the histological findings were consistent with the diagnosis of CNS vasculitis.

After diagnosis of CNS vasculitis, she was treated with oral daily cyclophosphamide (CYC) 2 mg/kg/day and an increased dose of prednisone for one month (MTX was discontinued). Her CNS dysfunction, muscle weakness, and cutaneous DM responded dramatically to CYC. Followup MRI 5 months after the start of CYC treatment showed unequivocal improvement compared with the initial MRI study, with a decrease in the abnormal T2 weighted signal in the frontal lobe white matter and markedly decreased punctate enhancement (Figure 4). Her DM entered remission 6 months into a one year course of daily CYC. Currently, 6 months after stopping CYC, she continues only prednisone 6 mg/day. Her muscle strength is normal, she has no signs of cutaneous DM, and she has no residual neurological dysfunction.

DISCUSSION

To our knowledge, this is the first report of CNS vasculitis occurring in an adult with DM. Vasculitis in other organ systems is known to occur in DM (e.g., in the retina, skin, muscle, testes, and gastrointestinal, GI, tract), and is an especially common complication of juvenile DM[3-10]. In 1966, Banker and Victor reviewed 8 fatal childhood cases of DM at postmortem and concluded that the fundamental pathologic change was an angiopathy, not only of the skin and muscle, but also of fat, GI tract, and small nerves[4]. We are aware of one case of biopsy proven CNS vasculitis in a 6-year-old girl with juvenile DM[11]. Two other cases of CNS dysfunction in juvenile DM have been reported, but neither was confirmed to be CNS vasculitis by angiogram or biopsy[12,13].

In DM, muscle histopathology reveals perivascular B cell and CD4+ T cells, accompanied by the deposition of late complement components (C5–C9, the membrane attack complex) in or near the vessels of affected muscles[1,2]. Damage to the intrafascicular capillaries occurs even before any evidence of muscle damage. This obliterative vasculopathy of the microvasculature is attributed to an immune complex mediat-

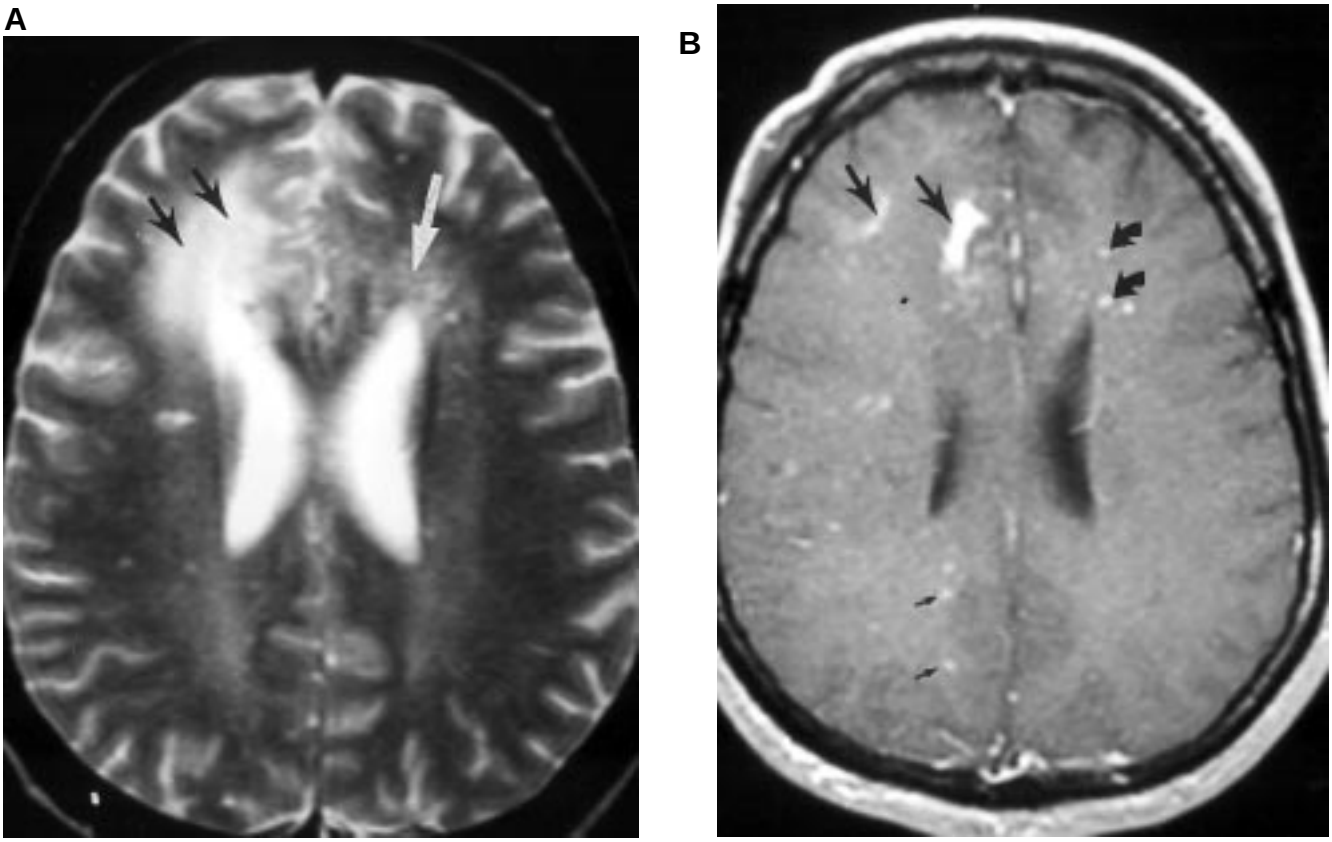

Figure 1. MR imaging at presentation. A. Axial T2 weighted spin-echo image (TR 3000/TE 80) depicts bright signal in frontal lobe white matter bilaterally, right (double arrows) more than left (single arrow). The bright regions are due to ischemia. B. Axial T1 weighted SE post-contrast image (500/32) shows multifocal enhancement, primarily within the frontal white matter (large straight arrows), but also in punctate regions throughout both hemispheres (small straight and curved arrows).

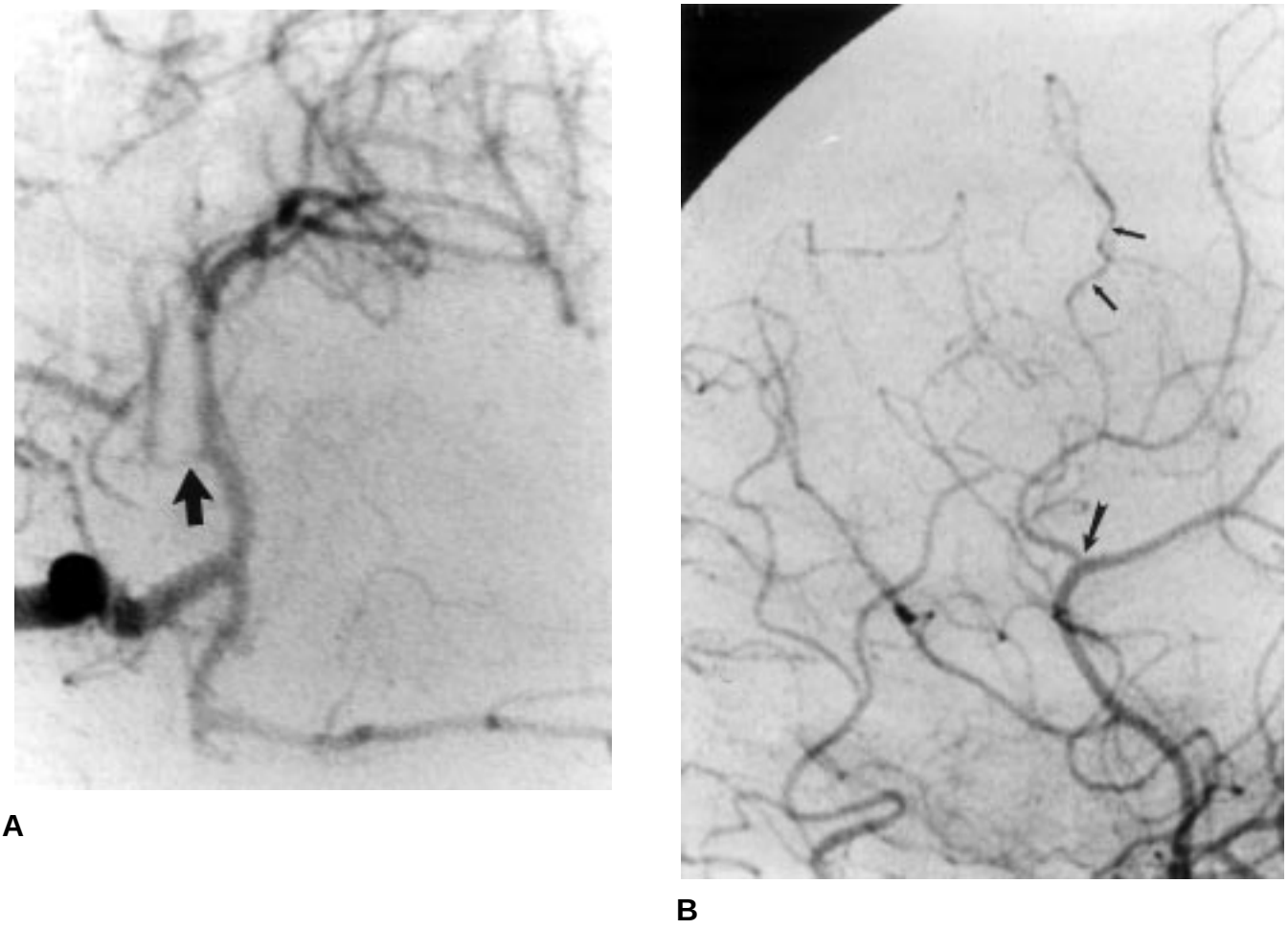

Figure 2. Cerebral angiography. A. Right common carotid angiography revealed a focal stenosis in the anterior temporal branch of the right middle cerebral artery (MCA) (arrow). Delayed filling of the more distal MCA segments was evident as a result of that stenosis. B. Normal bifurcation of the anterior cerebral arteries (ACA) into the pericallosal (inferior) and callosomarginal arteries shown for the purpose of orientation (large arrow). Two foci of narrowing within a distal ACA segment (small arrows). These findings are compatible with vasculitis.

ed mechanism in which complement plays a central role[2]. In light of the vasculocentric nature of DM and the known occurrence of vasculitis in other organs, it is intriguing that CNS vasculitis has never been reported in adults with this disorder[1,2,10].

In our patient, DM was partly suppressed but never truly controlled with the combination of prednisone, MTX, and HCQ. Refractory DM was manifested by the frequent requirement for increases in her prednisone dose to treat muscle weakness, the persistently active skin disease, and ultimately, the development of CNS vasculitis with a cerebral infarction.

The differential diagnosis of our patient's neurological presentation was broad. One possibility was MTX induced leukoencephalopathy. The radiographic findings in this case, including the extensive white matter involvement[14] and enhancement with contrast[15], are compatible with this diagnosis. The pathological findings of MTX leukoencephalopathy appear to be mediated by a necrotizing angiitis, consistent with the biopsy findings in our patient. However, MTX leukoencephalopathy generally occurs as a complication of the much higher doses of MTX used in the treatment of hematopoietic malignancies and sarcomas (e.g., at intravenous doses > 500 mg/m^2), and is particularly common after intrathecal administration[16]. Concomitant radiation therapy to the CNS increases the likelihood of MTX leukoencephalopathy. In contrast, leukoencephalopathy occurring with the far lower doses of MTX used to treat rheumatic diseases has not been reported. Moreover, our patient had been taking MTX for an entire year at the time of her presentation with CNS dysfunction.

Opportunistic infection was an alternative explanation. In particular, progressive multifocal leukoencephalopathy (PML), caused by the JC virus, complicates the treatment course in some patients with rheumatic conditions[17]. When occurring concomitantly with rheumatic conditions, PML is often mistaken for a CNS complication of the underlying disorder. The "heart of the gyrus" finding on our patient's first MR study (Figure 1) resembles PML radiologically, but the

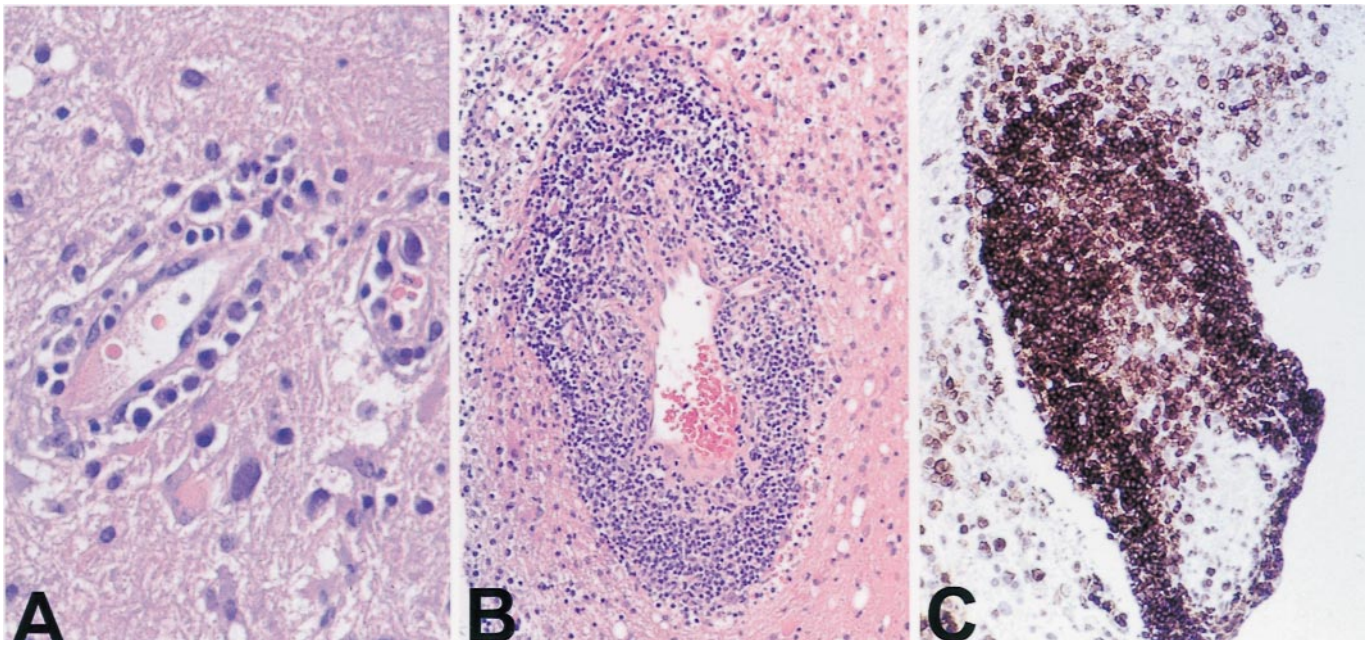

Figure 3. Brain biopsy. A. Histological section from the brain biopsy showing the infiltration by lymphocytes of a small blood vessel in the cerebral cortex (H&E; magnification ×400). B. Small blood vessel affected by a severe inflammatory reaction that extends to the perivascular space (magnification ×200). C. Immunocytochemical studies with anti-CD3 antibodies showing predominance of T lymphocytes in the blood vessel wall and perivascular space (magnification ×200).

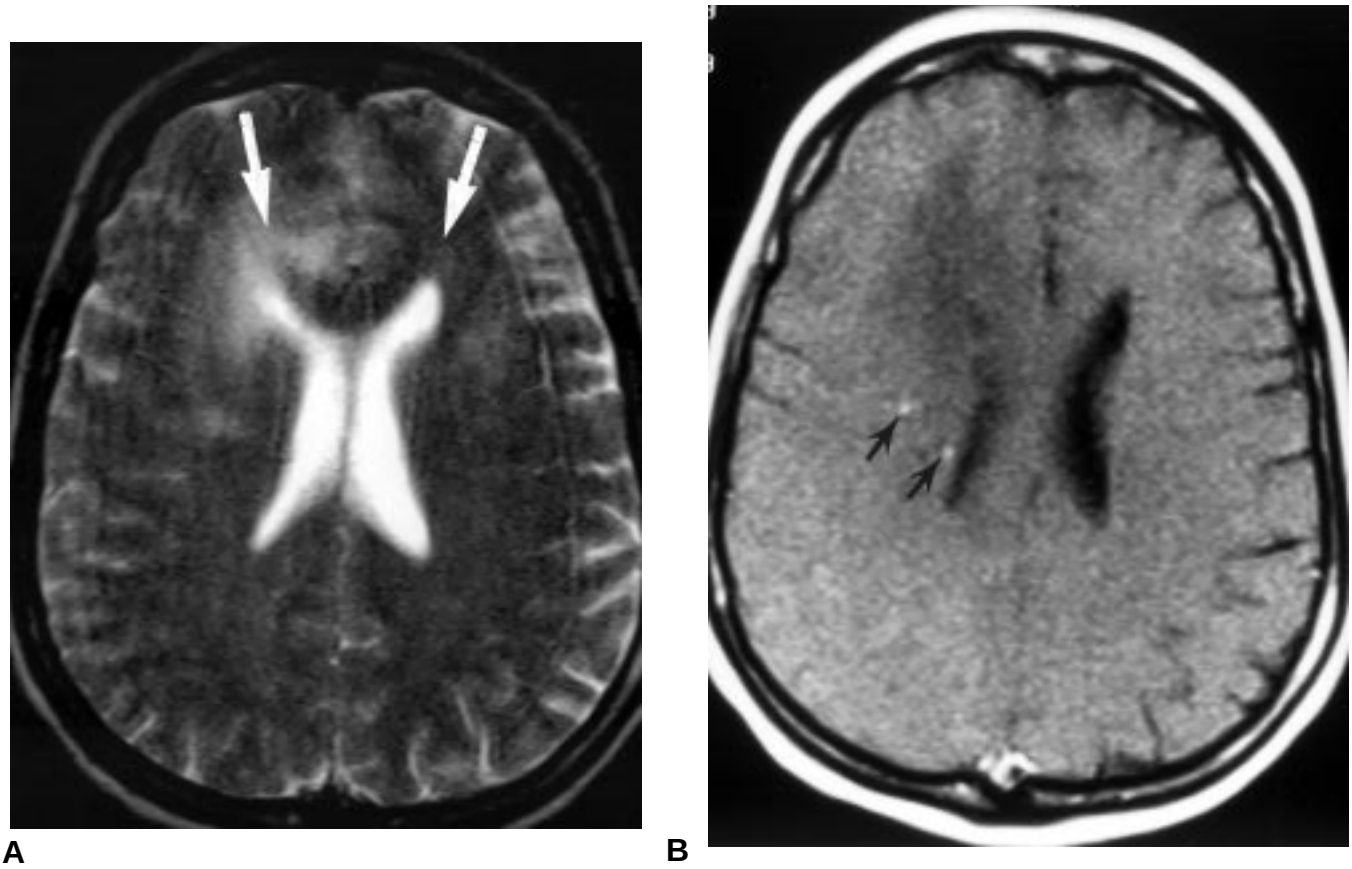

Figure 4. Followup brain MR imaging, 5 months after presentation. An axial T2 weighted spin-echo image (TR 8380/TE 134) shows a decrease in abnormal T2 signal in the frontal lobe white matter relative to the initial MR study (arrows). An axial T1 weighted post-contrast image (500/15) depicts markedly decreased punctate enhancement (arrows) compared with the initial MR study.

negative PCR assay for JC virus (performed on both CSF and brain tissue) as well as the negative immunocytochemical studies for papovavirus eliminate this possibility.

Finally, the subacute onset of cognitive decline punctuated by a tonic-clonic seizure is a common presentation of a cerebral malignancy. Because of the well established connection between malignancies and DM, we considered the possibility of a brain tumor[18-22]. In DM, malignancies occur in 10–15% of patients, either before or after the diagnosis of DM[8,23]. The types of malignancy associated with DM include lung cancer, various malignancies of the GI tract, and ovarian cancer[8,24]. To our knowledge, however, brain tumors have not been reported in association with DM. Furthermore, several radiologic features argued against a cerebral malignancy: the absence of mass effect; the presence of punctate enhancement (Figure 1B) as opposed to the uniform enhancement typical of tumors; and regression of this process over time in the absence of specific cancer therapy (Figures 4A, 4B).

The diagnosis of CNS vasculitis is perpetually challenging. Only half of patients with CNS vasculitis have abnormal lumbar punctures[25]. Even among cases confirmed by biopsy, angiograms may be normal in 40%[26]. The combination of angiography and MRI, however, usually detects abnormalities, particularly if serial studies are performed. A sound approach to patients with CNS vasculitis has been proposed[27], but a high index of clinical suspicion for this diagnosis is essential. Our case illustrates that CNS vasculitis may complicate cases of refractory DM.

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