Recovery from Rheumatoid Cerebral Vasculitis by Low-Dose Methotrexate

Tatsuharu Ohno, Isao Matsuda*, Hiroo Furukawa and Tadashi Kanoh**

We report the successful management of cerebral vasculitis in a 46-year-old woman with longstanding rheumatoid arthritis with low-dose methotrexate. She suddenly developed dysarthria and left hemiparesis. Magnetic resonance imaging disclosed ischemia of the right pons, and angiography demonstrated cerebral vasculitis of vertebro-basilar arteries. The vasculitis was refractory with high-dose steroid therapy, which had only transient clinical benefit, and evolution to the pontine infarction followed. Her clinical status showed marked improvement in association with recovery of the vascular abnormalities after the initiation of the methotrexate therapy.

Key words: rheumatoid arthritis, cerebral vasculitis, cerebral infarction

Introduction

While the central nervous system (CNS) is usually spared in rheumatoid arthritis (RA), several patients have been reported to suffer from CNS involvement. These manifestations result from various causes associated with the diversity of the disease process of RA (1). Cursory review of the literature revealed very rare cases of cerebral vasculitis in RA, usually with a fatal outcome (2-9). Here, we describe a patient with RA who developed cerebral infarction due to vasculitis of vertebro-basilar arteries, and showed striking clinical and angiographic recovery by low-dose methotrexate (MTX) therapy.

Case Report

A 46-year-old woman, with definite RA since the age of 30, was admitted to the hospital because of dysarthria and left hemiparesis of sudden onset. It had been well controlled with prednisolone (5 mg/day), piroxicam (10 mg/day), and sodium aurothiomalate (25 mg/week). Laboratory data in the outpatient clinic revealed a rheumatoid factor (RF) of 70.5-176 (normal <20) IU/ml, and C-reactive protein (CRP) of 0.3-0.7 mg/dl. Other serological, biochemical, hematological data and urinalyses were within the normal ranges.

On admission, her consciousness was mildly disturbed, and she had complaints of severe throbbing pain over the occiput, dysarthria and clumsiness of left fingers. Vital signs were normal. Neurological examination revealed hemiparesis and exaggerated deep tendon reflexes with Babinski's sign in the left. Involvement of cranial nerves was not evident. No sensory disturbance or cerebellar signs were present. Questionable nuchal stiffness was observed but not Kernig's sign. Routine laboratory data were as follows: erythrocyte sedimentation rate (ESR) 40 mm/h; hematocrit (Ht) 36.3%; white blood cell (WBC) count 6,400/µl with 67% neutrophils, 1% eosinophils, 5% monocytes, 27% lymphocytes; and 29.8×10⁴/µl platelets (PLT). Coagulation parameters, biochemical variables and urinalyses were within the normal ranges. RF was 79.9 IU/ml, and CRP was 0.5 mg/dl. A serological test for syphilis (VDRL), anti-nuclear antibody, anti-DNA antibody, anti-cardiolipin IgG antibody or lupus anticoagulant was negative. Serum IgG, IgM and IgA were 1,020, 108 and 282 mg/dl, respectively. Cryoglobulin was negative. Serum soluble immune complexes (1.0 µg/ml), CH50 (31 U), C3 (84 mg/dl), and C4 (35 mg/dl) were within the normal ranges. The optic fundus was normal. Lumbar cerebrospinal fluid (CSF) showed the initial and the final pressure of 220 and 160 mmH₂O, respectively, and 32 white cells/µl, all of which were lymphocytes. CSF glucose and protein were 51 and 62 mg/dl, respectively. Gram and acid-fast stains, routine culture, and fungal culture of the CSF were subsequently negative. Cryptococcal antigen on latex beads was negative. Complement fixation tests for herpes simplex and zoster were within the normal ranges. Soluble immune complexes (<1.0 µg/ml), IgG (4.0 mg/dl), and myelin basic
protein (1.3 ng/ml) of the CSF were within the normal ranges. Oligoclonal IgG bands in the CSF was not detected. Results of CSF cytology were negative for malignant cells. A magnetic resonance imaging (MRI) scan of the brain disclosed stenotic change of the basilar artery, and slightly increased signal intensity in the right side of the pons on T2-weighted images (T2-WI) in spite of the apparently normal signal in this area on T1-WI, suggesting cerebral ischemia. Cerebral angiogram demonstrated multiple discrete areas of segmental narrowing and dilatation of vertebro-basilar arteries. Maximum involvement was observed in the right vertebral artery, and paucity of blood flow in this area was noticed. Methyl-prednisolone (375 mg/day) and dextran 40 were administered. Figure 1 summarizes the clinical course of the patient.

In the subsequent several days, her general condition was stable. She became alert and did not complain of a headache. On the tenth hospital day, she became hypotensive and left hemiparesis occurred in addition to the exacerbation of left hemiparesis. The second MRI scan revealed an area of slightly decreased signal intensity on T1-WI at the right side of the pons. On T2-WI the signal of the lesion was intensified in relation to that of the intact part. Progressive ischemia of the right part of the pons was suspected. The basilar artery was severely stenotic with flow-enhancement due to slow blood flow on T1-WI (Fig. 2) (10). Administration of sodium ozagrel (40 mg/day), and continuous infusion of dopamine was resumed. On the 26th hospital day, her vital signs recovered and dopamine was withdrawn, but the neurological deficits remained unchanged. She then underwent a second angiographic examination. The four-vessel study disclosed progressive multiple segments of narrowing and dilatation involving bilateral carotid arteries as well as vertebro-basilar arteries, and markedly impaired cerebral blood perfusion. Maximum involvement was noticed again in the distal end of the right vertebral artery (Fig. 3). Methyl-prednisolone was tapered and withdrawn; it was replaced with prednisolone (50 mg/day), and MTX (5 mg/week). Aortography, celiac and renal angiographies performed on the 34th hospital day in search of systemic involvement of rheumatoid vasculitis, revealed no abnormalities. Prednisolone was tapered to 10 mg/2 days. Her vital signs remained stable, and dysarthria and left hemiparesis gradually improved. Left paresthesia also improved leaving residual numbness of the lateral side of the left forearm and foot. MRI scan performed on the 76th hospital day demonstrated decreased signal intensity at the right side of the pons on T1-WI, which was very high on T2-WI, suggesting completion of infarction. However, the diameter of the basilar artery was enlarged without flow-enhancement (Fig. 2). On the 86th hospital day, angiography showed marked improvement of cerebral vasculitis. Then, she was discharged to outpatient care with low-dose MTX (5 mg/week).

![Fig. 1. Clinical course of the patient showing the major symptoms, treatments, and laboratory data. The arrowhead with asterisk is the aortic, celiac, and renal angiography performed in search of systemic vasculitis.](image-url)
and prednisolone (10 mg/2 days).

Ten months after the episode, cerebral angiography performed for confirmation disclosed an almost normal appearance of vertebro-basilar arteries, and recovery of the cerebral blood flow (Fig. 3). CRP, RF and ESR after the episode remained relatively stable (<0.3–0.5 mg/dl, <20–34 IU/ml and 22–28 mm/h, respectively) without other serious abnormalities of laboratory data, and regular checkups with MRI and magnetic resonance angiography have disclosed no significant changes. She has been enjoying daily life as a housewife without the need for analgesics for more than a year and a half.

Discussion

In RA, the CNS may be affected by compressive dural nodules, rheumatoid pachymeningitis, vertebral subluxation, and hyperviscosity syndrome (1). While vasculitis occurs in only a minority of RA patients with aggressive disease and most
commonly consists of dermal manifestations, cerebral vasculitis rarely gives rise to neurological complications in RA (2–9, 11). Table 1 summarizes reports of rheumatoid cerebral vasculitis. The male to female ratio, mean age and mean duration (years) of the disease in these patients were 6 to 5, 53 and 16, respectively. Clinical signs and symptoms were abnormal mentation or alterations in the level of consciousness in 8, focal motor deficits in 6, seizures in 4, and peripheral neuropathy signs in 4 cases. CSF did not show a specific change for cerebral vasculitis. Vasculitis was verified at autopsy in 9 cases, 2 of which were associated with rheumatoid nodules. In 2 recent cases, including the present report, cerebral vasculitis was established by angiography which demonstrated the same abnormalities (11). Four specified cases were considered to show isolated cerebral vasculitis, and 4 other cases were associated with peripheral neuropathy, indicating systemic rheumatoid vasculitis.

Similar to the majority of previously reported cases, the present case had a long-standing history of RA, which required steroid therapy. The diagnosis of rheumatoid cerebral vasculitis was made by cerebral angiography. MRI scan qualitatively disclosed the injured area. Other causes of cerebral vasculitis
Table 1. Summary of Findings in 11 Cases of Rheumatoid Cerebral Vasculitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, Sex</th>
<th>Duration of RA</th>
<th>CNS signs &amp; symptoms</th>
<th>CSF findings</th>
<th>Autopsy findings of CNS</th>
<th>Diagnostic examination, &amp; other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirani &amp; Bennett 1951 (2) case 2</td>
<td>22 M ESR 14–36 mm/h</td>
<td>16 yr</td>
<td>Seizures, delirium</td>
<td>ND</td>
<td>Basal ganglionic arteritis &amp; softening</td>
<td>Widespread periarteritis nodosa</td>
</tr>
<tr>
<td>Kemper et al 1957 (3) case 3</td>
<td>63 F ESR 120 mm/h</td>
<td>18 yr</td>
<td>Auditory/visual hallucinations, slurred speech, right facial weakness, left hemiparesis</td>
<td>ND</td>
<td>Fusiform basilar artery aneurysm, right pontine infarct, necrotizing arteritis of basilar artery &amp; chorid plexus</td>
<td>Severe peripheral neuropathy</td>
</tr>
<tr>
<td>Kemper et al 1957 (3) case 3</td>
<td>64 F SCA 1:8, 192</td>
<td>30 yr</td>
<td>ND</td>
<td>ND</td>
<td>Cerebral arteritis</td>
<td>ND</td>
</tr>
<tr>
<td>Johnson et al 1959 (5) case 1</td>
<td>37 M SCA (+)</td>
<td>20 mo</td>
<td>Seizures</td>
<td>ND</td>
<td>Necrotizing arteritis of meningeal arteries</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Sokoloff &amp; Bunim 1959 (4) case 2</td>
<td>63 ESR 1:8</td>
<td>3 yr</td>
<td>Loss of consciousness, incoherence, confusion, left hemiparesis</td>
<td>ND</td>
<td>Meningocerebral vasculitis, extensive cerebral infarction</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Steiner &amp; Gellboom 1959 (6) case 2</td>
<td>62 M ND</td>
<td>20 y</td>
<td>Confusion, coma, diminished pupillary reflex, superficial &amp; deep tendon reflexes</td>
<td>ND</td>
<td>Vasculitis with secondary ischemic changes in cortex and white matter of the cerebrum, RN in dura and in subarachnoid space</td>
<td>Clinical neurological manifestations probably due to bacterial meningitis</td>
</tr>
<tr>
<td>Ouyang et al 1967 (7)</td>
<td>58 F ESR 102 mm/h, latex (+)</td>
<td>30 yr</td>
<td>Confusion, loss of consciousness, seizures, right hemiparesis</td>
<td>Pressure 190 mm H₂O, 3 WBC &amp; 760 RBC/ml, protein 80 mg/dl, glucose 58 mg/dl, chloride 121 mEq/L</td>
<td>Subarachnoid &amp; parenchymal cerebral vasculitis, RN in leptomeninges</td>
<td>No vasculitis outside CNS, abnormal EEG in the left</td>
</tr>
<tr>
<td>Ramos &amp; Mandybur 1975 (8)</td>
<td>63 M SCA 1:448, ESR 4–58 mm/h, latex (+)</td>
<td>1 yr</td>
<td>Gerstman syndrome, dementia, blindness</td>
<td>Pressure 130 mm H₂O, no cells, protein 133 mg/dl, glucose 57 mg/dl</td>
<td>Necrotizing meningo-cerebral vasculitis with amyloid deposits, multiple small infarcts</td>
<td>Abnormal EEG, normal brain scan, angiogram &amp; PEG</td>
</tr>
<tr>
<td>Watson et al 1977 (9)</td>
<td>54 F ESR 80–120 mm/h, latex (+)</td>
<td>20 yr</td>
<td>Dysphasia, left 6th &amp; 7th nerve palsies, left arm &amp; leg ataxia, right hemiparesis</td>
<td>Normal cell count, protein 117 mg/dl</td>
<td>Old left frontal &amp; pontine, &amp; new right frontal &amp; pontine hemorrhages, necrotizing arteritis in cerebrum, pons, cerebellum &amp; spinal cord</td>
<td>No vasculitis outside CNS</td>
</tr>
<tr>
<td>Gobernado et al 1984 (10)</td>
<td>48 F ESR 30 mm/h</td>
<td>22 yr</td>
<td>Loss of consciousness, seizures, right frontoparietal headache, diplopia, generalized hyper-reflexia, confusion</td>
<td>11 WBC/ml, protein 40 mg/dl, glucose 56 mg/dl</td>
<td>Alive with clinical recovery, no information on follow-up examinations</td>
<td>Abnormal EEG, a small hemorrhage in the right temporal lobe multiple areas of low density in both hemisphere on CT, vasculitis on angiogram (MCA, PCA, PICA)</td>
</tr>
</tbody>
</table>
were eliminated as far as possible based on past history, physical findings, clinical data, laboratory studies, and response to the therapy. In contrast to the case of Gobernado et al (11), cerebral vasculitis of the present case was intractable with steroids, resulting in pontine infarction and deterioration of angiographic abnormalities. Rheumatoid cerebral vasculitis has been suggested to be related to steroid therapy (3, 5). Moreover, the published observations of cases of rheumatoid cerebral vasculitis, in whom RA had been treated with steroids, revealed a poor prognosis (2–9). Steroid therapy over a long period of time might have affected cerebral vasculitis in the present case.

Although MTX is a highly effective second-line agent and is widely used for RA, its use in rheumatoid vasculitis is controversial. Some reports have discussed the effectiveness of MTX for cutaneous vasculitis (12, 13), and aggravation of systemic rheumatoid vasculitis after discontinuation of MTX (14). Other reports have described accelerated nodulosis and vasculitis during MTX therapy for rheumatoid arthritis (15, 16). In the present patient, on follow-up angiograms cerebral vasculitis was clearly shown to be improved with low-dose MTX therapy. Low-dose MTX therapy may be a treatment of choice in rheumatoid cerebral vasculitis, if it is intractable with steroids.

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References