

[CASE REPORT]

Possible Cerebral Vasculitis in a Case with Rheumatoid Arthritis

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Abstract:

Cerebral rheumatoid vasculitis (CRV) is a rare, fatal, and diagnostically challenging disorder. We herein report an 81-year-old woman with a 4-year history of rheumatoid arthritis who presented with a fever, progressive disturbance of consciousness, high level of rheumatoid factor, and hypocomplementemia. The enhancement of the perforating branches in the left middle cerebral artery led us to suspect CRV. A brain biopsy could not be performed. After we intensified steroid therapy, the size of the cerebral lesions temporarily decreased. However, recurrence in the left frontal lobe occurred one month later, and the patient subsequently died. Early intensive treatments may be needed for CRV.

Key words: cerebral rheumatoid vasculitis, rheumatoid factor, hypocomplementemia, brain biopsy

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Introduction

Approximately 1-5% of patients with rheumatoid arthritis (RA) present with vasculitis in the small and middle vessels, called “rheumatoid vasculitis (RV)” (1). RV often occurs in patients with long-standing RA and a high level of rheumatoid factor (2). Although RV is rare now that treatments for RA have progressed, it remains fatal (3). RV is usually found in the skin and peripheral nerves and rarely in the brain (4). Cerebral RV (CRV) is a rare and diagnostically challenging disorder that often requires an invasive brain biopsy for a definite diagnosis.

We herein report a case of possible CRV with a refractory and fatal course.

Case Report

An 81-year-old woman with a 4-year history of RA was admitted to our hospital with a fever and progressive disturbance of consciousness that had started 2 days earlier. She had been taking prednisolone (5 mg per day) and methotrexate (6 mg per week) for 4 years. She presented with a fever (39.2°C), disturbance of consciousness (Glas-

gow Coma Scale E2 V1M4), Kernig’s sign, and right hemiparesis. There were no signs of scleritis, swelling or deformation of the hand joints, oral or genital ulcer, or eruption that would suggest vasculitis.

Laboratory studies showed an increase in the white blood cell count (9,000/ μ L), C-reactive protein (0.99 mg/dL) and erythrocyte sedimentation rate (73 mm/h), high levels of rheumatoid factor (829 IU/mL) and anti-cyclic citrullinated peptide antibody (above 500 U/mL), and hypocomplementemia (C3 61 mg/dL, C4 9 mg/dL). Furthermore, the patient was negative for anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), beta-D glucan, cryptococcus and aspergillus antigens, and varicella-zoster virus IgM antibody. Human leukocyte antigen typing was not evaluated. A cerebrospinal fluid (CSF) examination revealed an increase in cells (70/mm³, polynuclear dominant). In addition, the level of proteins was within the normal range, and herpes simplex virus DNA was not present in the CSF. The levels of soluble interleukin-2 receptor were normal in both the serum and CSF.

Carotid ultrasonography was not evaluated. Whole-body computed tomography showed no malignancy or abnormal findings of the aorta. Contrast-enhanced brain magnetic resonance imaging (MRI) revealed multiple small ischemic

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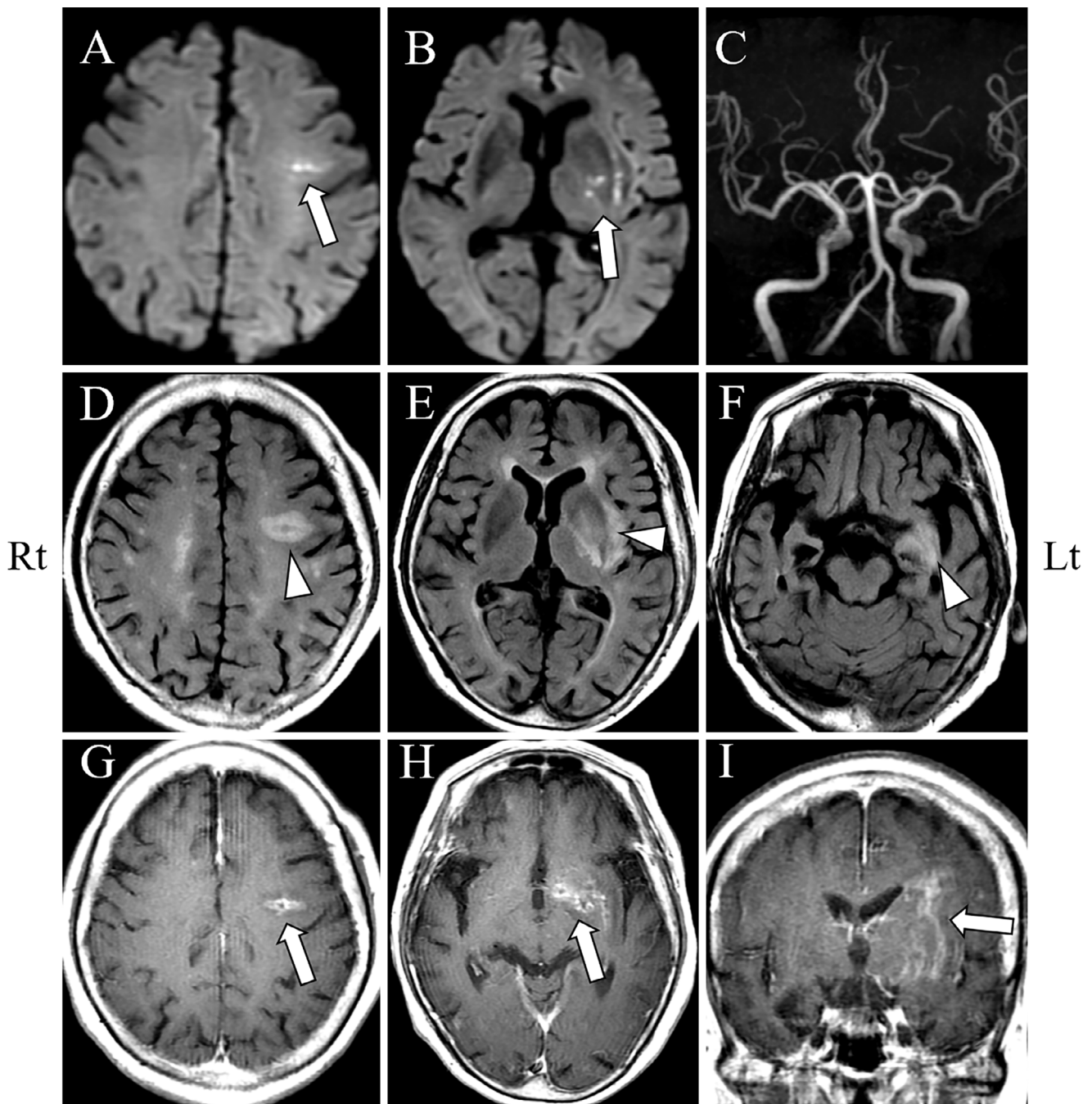


Figure 1. Brain magnetic resonance imaging (MRI) findings on admission. Axial diffusion-weighted brain MRI on admission shows multiple small high intensity lesions in the left frontal subcortex and basal ganglia (A, B, arrows). Edematous changes in the frontal lobe, basal ganglia, and left medial temporal lobe are also observed (D-F, arrowheads). Moreover, axial contrast-enhanced T1-weighted brain MRI shows ring-enhanced lesions in the left frontal subcortex and hypothalamus (G, H, arrows), and left lenticulostriate arteries are enhanced in the coronal section (I, arrow). Neither stenosis nor occlusion in the cerebral vessels were observed by magnetic resonance angiography (C).

lesions in the left subcortex of the frontal lobe and basal ganglia, an edematous lesion in the left medial temporal lobe, and an enhancement of the left lenticulostriate arteries. No stenosis or occlusion of the cerebral vessels was observed (Fig. 1). A random skin biopsy showed no vasculitis and lymphoma cells. A brain biopsy could not be performed because her family did not provide consent.

Because of the high level of rheumatoid factor and anti-cyclic citrullinated peptide antibody, hypocomplementemia, and the enhancement of the cerebral vessels, we suspected cerebral RV and initiated treatment with a high dose of prednisolone (45 mg per day) on day 11. The fever quickly abated, and her disturbance of consciousness slightly improved, but the drowsiness remained, which prevented her

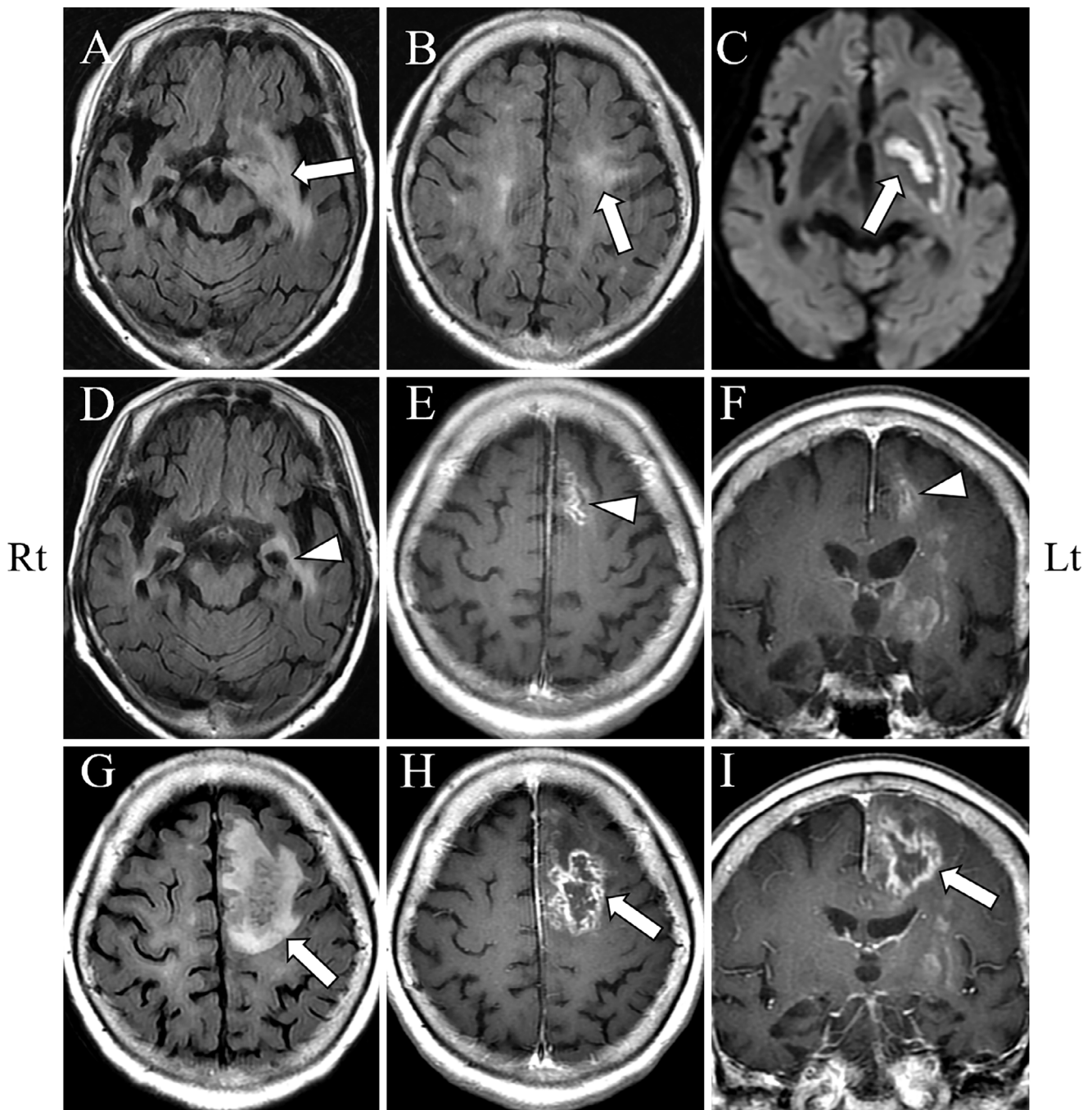


Figure 2. Brain magnetic resonance imaging findings after treatment. On day 16, although the size of the left frontal lesion decreases, the left temporal lesion increases, and ischemic lesions remain in the left hypothalamus and basal ganglia (A-C, arrows). While the left temporal lesion decreases on day 29 (D, arrowhead), the recurrent lesion appears in the left frontal lobe (E, F, arrowheads), which shows a significant enlargement on day 36 (G-I, arrows).

from eating and leaving the bed. After treatment, laboratory studies revealed an improvement in the level of rheumatoid factor and hypocomplementemia. MRI showed a partial improvement and clarification of the left temporal edematous lesion (Fig. 2A-C). Because of her response to steroid therapy, the dose of prednisolone was lowered to 35 mg per day on day 25. On day 29, the left temporal lesion and enhancement of the perforated branches decreased, while a left medial frontal lesion newly appeared (Fig. 2D-F).

She vomited and presented with a fever and coma again on day 35. The left frontal lesion was markedly increased and showed ring-enhancement (Fig. 2G-I). We refrained from additional cyclophosphamide therapy, considering her poor performance status. An increase in the dose of prednisolone to 45 mg per day did not improve the patient's fever or coma, and she subsequently died on day 39. Her family did not provide consent for a pathological autopsy. The patient's clinical course is shown in Fig. 3.

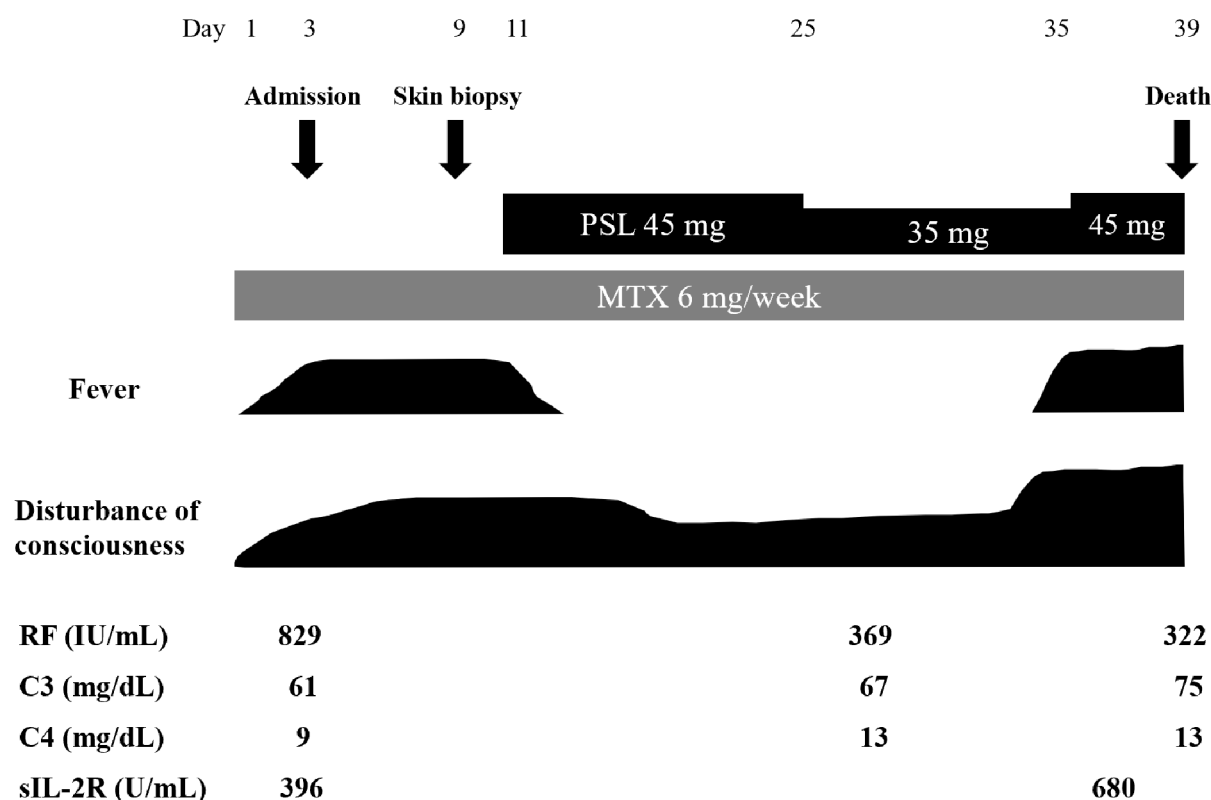


Figure 3. Clinical course. We started treatment with a high dose of prednisolone on day 11. Although fever quickly abated, the improvement in the disturbance of consciousness was limited. On day 35, high fever and coma reappeared, and the patient died on day 39. PSL: prednisolone, MTX: methotrexate, RF: rheumatoid factor, sIL-2R: soluble interleukin-2 receptor

Discussion

In the present case, the high level of rheumatoid factor and hypocomplementemia indicated that the etiology may have been related to RV, and due to the enhancement of the cerebral vessels, we diagnosed her with possible CRV. Oral and genital ulcers indicating Behçet's disease and the dizziness and deafness characteristic of Cogan's syndrome were not seen. Furthermore, we did not suspect giant cell arthritis because there was no swelling of the temporal arteries or abnormal findings of the aorta. Although laboratory studies did not detect ANCA, the lack of a pathological diagnosis could not completely deny ANCA-related vasculitis.

Twenty-six cases of adult onset CRV have been reported thus far (5-27), as shown in Table. Although the mean duration of RA was long (15.9 years), cases of RA lasting less than 10 years, such as the present, are not rare (7 cases, 29%), and in such cases, the level of rheumatoid factor was relatively high (mean 585 IU/mL). Regarding radiological findings, almost the same rate of patients presented with bilateral lesions as with unilateral lesions, and most lesions were localized in the subcortex or white matter. Thirteen cases have been pathologically diagnosed, which included

only three cases with an antemortem diagnosis. This suggests that the antemortem diagnosis of this disease is quite challenging, as demonstrated in our case. Immunotherapies reportedly intensified or added after the neurological onset included steroid therapy alone in 10 cases and combined therapy in 11 cases. While steroid therapy alone resulted in a mortality rate of 50%, all cases treated with combined therapy including cyclophosphamide showed improvement.

Previous case reports have indicated that CRV can occur with short-standing RA, and combined immunotherapy with cyclophosphamide can improve the disease condition.

The present case also has the limitations about the diagnosis, since intravascular malignant lymphoma (IVL) and methotrexate-associated lymphoproliferative disorders (MTX-LPDs) could not be excluded because of the lack of a pathological diagnosis. The partial response to steroid therapy was not inconsistent with IVL, and the history of MTX may have resulted in MTX-LPDs. However, the patient's hypocomplementemia could not be explained by IVL or MTX-LPDs, indicating an etiology related to RV.

In conclusion, we encountered a case of possible CRV with a refractory and fatal course. Combined immunotherapy including cyclophosphamide may be suitable in cases of CRV.

Table. Cases of Rheumatoid Arthritis with Cerebral Vasculitis.

Age, Sex	Duration of RA (years)	ESR (mm/h)	RF (IU/mL)	Neurological symptom	Abnormal lesions in CT or MRI	Pathological findings of brain	Immunotherapies intensified or added after neurological onset	Outcome	Reference
22, M	16	36	ND	Seizure, delirium	ND	Basal ganglionic arteritis	ND	Death	(5)
64, M	30	ND	ND	ND	ND	Cerebral arteritis	Steroid	Death	(6)
63, F	18	120	ND	Hallucination, slurred speech, right facial weakness, left hemiparesis	ND	Necrotizing arteritis of basilar artery and choroid plexus	Steroid	Death	(7)
37, F	1.7	ND	ND	Seizure	ND	Necrotizing arteritis of meningeal arteries	None	Death	(8)
63, M	3	ND	ND	Loss of consciousness, left hemiparesis	ND	Meningocerebral vasculitis	Steroid	Death	(8)
62, M	20	ND	ND	Coma, confusion	ND	Vasculitis with secondary ischemic changes in cortex and white matter of the cerebrum	None	Death	(9)
58, F	30	102	ND	Loss of consciousness, seizure, right hemiparesis	ND	Parenchymal cerebral vasculitis	Steroid	Death	(10)
54, F	20	120	ND	Dysphasia, left facial palsy, right hemiparesis	ND	Necrotizing arteritis in cerebrum, pons, cerebellum	Steroid	Death	(11)
63, M	1	58	ND	Gerstman syndrome, dementia, blindness	ND	Necrotizing meningocerebral vasculitis	ND	Death	(12)
50, F	6	ND	ND	Left hemiparesis	Left insular cortex and bilateral fronto-parietal white matters	NE	Steroid	Improvement	(13)
48, F	22	30	ND	Loss of consciousness, seizure, diplopia	Bilateral cerebral white matters	NE	Steroid	Improvement	(14)
46, F	16	40	79.9	Drowsiness, dysarthria, left hemiparesis	Right side of the pons	NE	Steroid+MTX	Improvement	(15)
55, F	7	58	ND	Dysarthria	Right side of the pons and parietal subcortex	Perivascular inflammatory infiltration and fibrosis in the vessels of the white matter	Steroid+CPA	Improvement	(16)
64, F	7	116	41.5	Delirium, aphasia, apraxia	Bilateral temporal and parietal subcortices	NE	Steroid	Improvement	(17)
51, F	39	70	ND	Confusion, left hemiparesis	Bilateral cerebral white matters	Fibrinoid necrosis, perivascular fibrosis and lymphocytic infiltration in the small arteries of the white matter	Steroid+IVIg	Death	(18)
49, F	10	50	127.4	Aphasia, hemianopia	Left temporal white matter	NE	Steroid+CPA	Improvement	(19)
70, F	ND	ND	57.6	Seizure	Left occipital subcortex	NE	Steroid+CPA	Improvement	(19)
59, F	20	135	ND	Diplopia, gait disorder	Bilateral periventricular subcortices	NE	Steroid+CPA	Improvement	(20)
63, F	12	ND	ND	Confusion, seizure, quadriparesis	Right parietal subcortex	NE	Steroid+CPA	Improvement	(21)
71, F	15	79	ND	Dysarthria, left hemiparesis	Right frontal, parietal and temporal white matter	Necrotizing and lymphocytic vasculitis in both meningeal and cerebral parenchyma	Steroid	Improvement	(22)
52, F	9	27	51.2	Headache	Bilateral frontal and parietal subcortices	NE	MTX	Improvement	(23)
47, F	11	70	ND	Mental status change, seizure	Bilateral frontal, parietal, hippocampal and cerebellar white matters	NE	Steroid+CPA+IVIg	Improvement	(24)
52, F	20	36	ND	Confusion, bilateral visual field defects, dysphasia, ataxia and left hemiparesis	Bilateral occipital cortices	Lymphocytic infiltration and focal vessel wall disruption	Steroid+CPA	Improvement	(25)
30, F	20	64	42.9	Left facial and upper extremity weakness	Bilateral frontal white matters	NE	Steroid+AZA	Improvement	(26)
52, M	29	116	82.9	Speech difficulty, right upper extremity weakness	Left temporal subcortex and bilateral parietal white matters	NE	Steroid+CPA	Improvement	(26)
61, F	ND	ND	ND	Loss of consciousness	Bilateral periventricular white matters, hippocampal gyri	NE	Steroid	Improvement	(27)
81, F	4	73	829	Drowsiness, right hemiparesis	Left frontal subcortex, hippocampus, hypothalamus and basal ganglia	NE	Steroid	Death (partial improvement)	Present case

RA: rheumatoid arthritis, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, CT: computed tomography, MRI: magnetic resonance imaging, ND: not described, NE: not evaluated, MTX: methotrexate, CPA: cyclophosphamide, IVIg: intravenous immunoglobulin, AZA: azathioprine

The authors state that they have no Conflict of Interest (COI).

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