

A case of 'lymphomatosis cerebri' diagnosed in an early phase and treated by whole brain radiation: case report and literature review

Ryuichi Kanai · Makoto Shibuya · Takashi Hata ·
Makoto Hori · Kenichi Hirabayashi · Tadashi Terada ·
Koji Fujii

Received: 23 April 2007 / Accepted: 11 June 2007
© Springer Science+Business Media B.V. 2007

Abstract 'Lymphomatosis cerebri' (LC) is a term indicating a diffusely infiltrating form of primary central nervous system lymphoma (PCNSL) without evidence of a mass lesion. Not infrequently, diagnostic confusion is caused by its presentation on cranial magnetic resonance images (MRI), which is characterized by diffuse leukoencephalopathy without contrast enhancement. In this report, we describe a 53-year-old, immunocompetent man who had an insidiously progressive dementia and right weakness. On serial MRI in 4 months duration, diffuse white matter lesions without contrast enhancement gradually progressed, which was clinically consistent with his worsening condition. Biopsy specimen demonstrated non-destructive, diffusely infiltrating, large B-cell lymphoma, diagnosing LC. After the biopsy, corticosteroids were initiated, which dramatically alleviated his symptoms. Afterwards, he was treated by whole brain irradiation (total

36Gy) and discharged without noticeable deficits. Diagnosis of LC requires additional examinations generally not performed in the other white matter disorders. In suspected cases, biopsy should be performed to avoid deferring adequate cytostatic treatment.

Keywords Leukoencephalopathy · Lymphomatosis cerebri · Magnetic resonance imaging · Primary CNS lymphoma · White matter dementia

Introduction

Primary central nervous system lymphoma (PCNSL) usually presents with clinical and neuroimaging findings consistent with focal or multifocal, isolated mass lesions. In immunocompetent patients, such lesions are almost invariably contrast enhancing on magnetic resonance imaging (MRI) [1–6]. Very rarely, the disease manifests as a diffuse infiltrating form without evidence of a mass lesion, referred to as 'lymphomatosis cerebri' (LC) [7–10]. Clinically, LC typically presents with a rapidly progressive dementia and unsteadiness of gait [7, 9, 10]. A characteristic MRI finding of LC is diffuse leukoencephalopathy in both hemispheres, which is assumed to be caused by widespread infiltration of the cerebral white matter by lymphoma cells, but those lesions show no contrast enhancement [7, 9]. Thus, clinical presentation and MRI features resemble other white matter disorders, and hence often cause diagnostic confusion with suspected diagnosis of Binswanger's disease (subcortical ischemic vascular dementia), infectious leukoencephalitis, or neoplasms such as gliomatosis cerebri [7, 9–13]. Here, we report a case of LC which slowly progressed both clinically and radiographically during 4 months follow-up. At first, white

R. Kanai (✉) · K. Fujii
Department of Neurosurgery, Shizuoka City Shimizu Hospital,
Shizuoka, Japan
e-mail: ryuichi@kj9.so-net.ne.jp

M. Shibuya
Department of Pathology, Hachioji Medical Center, Tokyo
Medical University, Tokyo, Japan

T. Hata · M. Hori
Department of Neurology, Shizuoka City Shimizu Hospital,
Shizuoka, Japan

K. Hirabayashi
Department of Pathology, School of Medicine, Tokai University,
Kanagawa, Japan

T. Terada
Department of Pathology, Shizuoka City Shimizu Hospital,
Shizuoka, Japan

matter lesions were asymmetric and accentuated in the left on MRI, but those lesions progressed bilaterally until almost symmetric. Biopsy specimen confirmed the diagnosis. Corticosteroids greatly improved his symptoms. After whole brain irradiation, he was discharged with oral corticosteroids.

Case report

This 53-year-old, right-handed, otherwise healthy man had a several month history of insidious personality changes and forgetfulness. At initial presentation, he was alert and complained of general fatigue, dizziness, and clumsiness of the right foot. The first MRI showed asymmetric diffuse white matter hyperintensity lesions that were noted in the left on T2-weighted or FLAIR images (Fig. 1A, B). Those lesions were isointense to slightly hypointense on T1-weighted images, and also involved the brain stem (not shown). On diffusion-weighted imaging (DWI), the lesions were slightly hyperintense (not shown). MRI angiography was normal. Demyelinating diseases such as multiple sclerosis, or degenerative disorders were suspected, and he was followed carefully in an outpatient basis. One month later, the second MRI was taken with contrast medium

(gadolinium (Gd)). Neither mass effect nor enhancement was apparent on a postcontrast study. Disorientation and right weakness had slowly developed during the next two months, and finally at 4 months after initial presentation, he was hospitalized with gait disturbance. On admission, he was slightly disoriented. Neurological examination revealed no apparent deficits other than weakness of the right extremities. Cerebrospinal fluid (CSF) examination showed a slightly increased protein (52 mg/dl, normal 15–40 mg/dl) and cell count (9/ μ l, normal <5/ μ l). On CSF cytology, numerous lymphoid cells were present, but no atypia was suggested. There was IgM synthesis in the CSF. Neither viral antibodies nor bacteria could be found in CSF. Circulating immune complexes containing IgM (48 mg/dl, normal 35–220 mg/dl) were within normal limits. Extensive microbiological serology including testing for HIV was unremarkable. On the third cerebral MRI, the size of white matter lesions significantly enlarged, and those were recognized as almost symmetric on T2-weighted or FLAIR images (Fig. 1C, D). There was still no contrast enhancement (Fig. 1E, F). On whole body positron emission tomography (PET) with fluor-desoxy-glucose (FDG), abnormal FDG uptake was observed neither in the trunk nor in the extremities. Clinically, the disease slowly, but steadily progressed even during the several days in

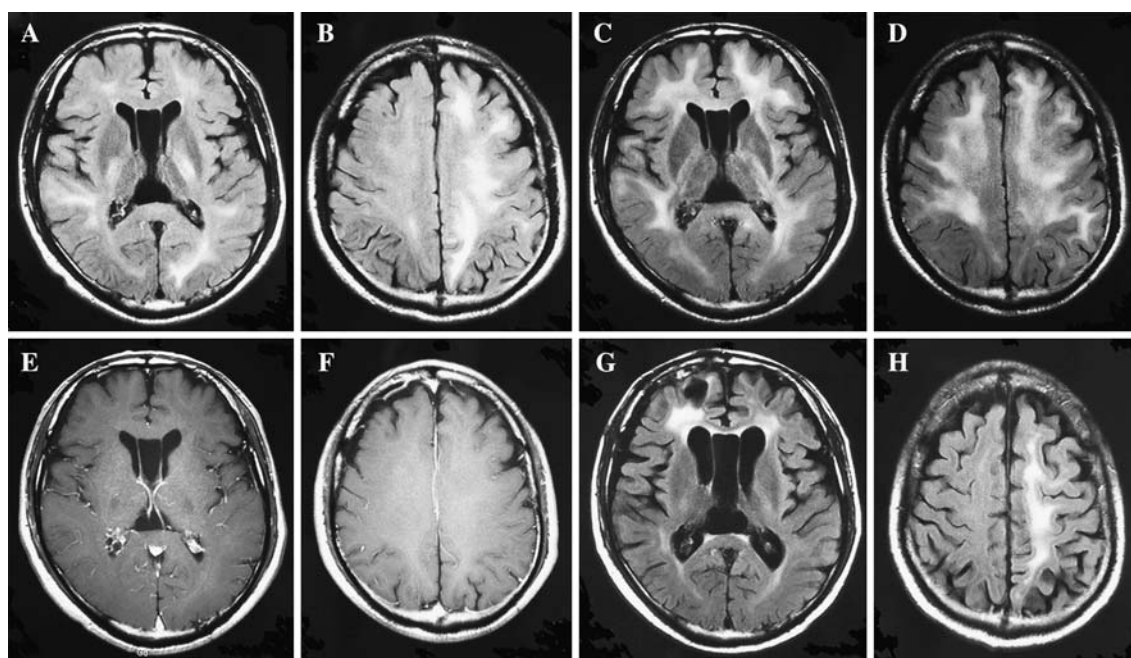


Fig. 1 (A, B) Cerebral MRI at initial presentation, FLAIR-weighted images showing pathological signal hyperintensities in the white matter of both hemispheres. Those lesions were accentuated in the left side. (C–F) MRI at admission (4 months from initial presentation). C/ D: FLAIR-weighted images at corresponding planes to A/B. Compared with the first MRI (A/B), white matter lesions markedly progressed, and appear almost symmetric. Note that those lesions now

involve the tip of the right frontal lobe, which was partially resected at the operation. E/F: T1-weighted image with Gd at the corresponding planes to C/D showing the absence of contrast enhancement in parenchyma. (G, H) The third MRI (FLAIR-weighted images corresponding to A/B) taken at the completion of radiotherapy, showing regression of white matter lesions

hospitalization. Because a definitive diagnosis was not yet reached, an open biopsy of the nondominant (right) frontal lobe was performed 4 months after symptom onset. Biopsy specimen showed diffuse infiltration of large-sized neoplastic lymphoid cells with B-cell lineage. He was given a trial of high-dose steroids (intravenous methylprednisolone, 1 g daily, for three days), which was clearly successful in improving the patient's condition. Afterwards, oral corticosteroids were started, and then tapered. In the meantime, since consent to extensive chemotherapy was not obtained, the patient was treated by whole brain irradiation (fractionated, 2Gy/day, total 36Gy). MRI taken after completion of radiotherapy showed shrinkage of high intensity lesions (Fig. 1G, H). He was discharged with maintenance dose of prednisolone (10 mg/day) without apparent deficits. On MRI taken 5 months later, white matter changes were still recognized, but further shrank, and the size of the ventricles was enlarged (not shown). He has been clinically stable for 11 months after biopsy.

Pathological findings

The biopsy specimen reveals increased cellularity in the white matter without apparent destructive changes (Fig. 2A, B). Atypical large-sized cells are diffusely scattered in the white matter with irregular shaped-nuclei and prominent

nucleoli (Fig. 2C). The atypical cells are not cohesive, and did not form a mass or perivascular concentric accumulation. Mitotic figures are scant in number. No atypical cells are found in the vascular lumina. In association with atypical cells in the white matter, observed are infiltration of small-sized reactive lymphoid cells and proliferation of numerous microglia with occasional rod-shaped nuclei. In comparison with conventional malignant lymphoma of the brain, reactive astrocytes appear to be less in number (Fig. 2E). The gray matter is rarely involved by the atypical cells.

Immunohistochemically, the atypical cells were positive for CD20, CD45 and CD79a, and some are weakly positive for MUM-1 in the nuclei (Fig. 2D). Ki-67 antigen positive cells are numerous (Ki-67 labeling = 30%). In contrast, they were negative for CD3, CD5, CD10, bcl-2, bcl-6, CD21, CD68, Olig2, or glial fibrillary acidic protein (GFAP). Infiltration of CD3, CD45 and CD45RO-positive small-sized lymphoid cells without atypia is discerned in the white matter and in the perivascular region. Iba-1 and CD68-positive microglia were diffusely present (Fig. 2F).

The atypical cells are morphologically and immunohistochemically similar to those seen in diffuse, large B-cell lymphoma cells. Since the tumor cells are scattered exclusively in the matter without mass formation, a pathological diagnosis of lymphomatosis cerebri was made.

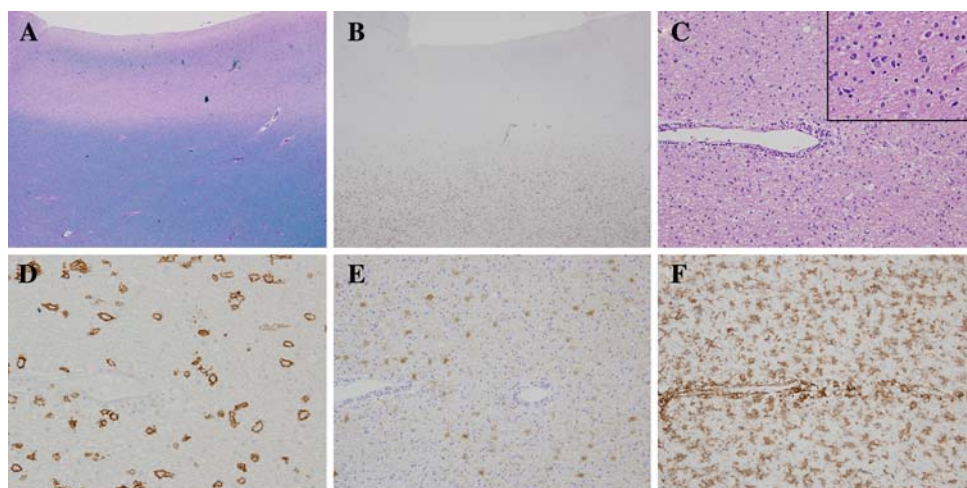


Fig. 2 (A) Hematoxylin and eosin with luxol fast blue staining shows preserved myelin structure in the white matter. (original magnification $\times 1.25$). (B) Immunohistochemical study reveals scattering infiltration of CD20 positive cells in the white matter without mass formation, whereas the tumor cells are rarely infiltrating in the gray matter (original magnification $\times 1.25$). (C) Hematoxylin and eosin staining in the white matter discloses scattering infiltration of atypical cells with irregular-shaped nuclei with occasional prominent nucleoli. Neither intravascular tumor cell growth nor perivascular tumor cell cuffing is identified. Accumulated small-sized lymphoid cells around

the blood vessel are mainly composed of CD3 positive T-cell lineage reactive cells (Data not shown). Inset: Observed are neoplastic lymphoid cells, small-sized reactive lymphoid cells, reactive astrocytes and microglia including rod-shaped nuclei. (original magnification $\times 10$, inset $\times 40$) (D) CD20 positive cells are diffusely infiltrating in the white matter. (original magnification $\times 10$) (E) GFAP positive reactive astrocytes are not prominent in the white matter. (original magnification $\times 10$) (F) Iba-1 staining shows numerous microglial proliferation in the brain tissue. (original magnification $\times 10$)

Table 1 Reported cases of lymphomatosis cerebri demonstrated by MRI in immunocompetent patients

| Author and year | Patient age (year), sex | Clinical presentations | Sites of involvement by MRI | Steroid administration (and response) | Treatment (Chemotherapy/radiation therapy) | Patient outcomes |
|-------------------------|-------------------------|--|---|--|---|--|
| Matsumoto et al. (1995) | 42, female | General fatigue, disorientation | Bilateral cerebral white matter, basal ganglia, brain stem | Betamethasone 1 mg/day, used as maintenance dose | Chemotherapy (cyclophosphamide, vincristine, adriamycin), ineffective | Died, 5 months later |
| Terae and Ogata (1996) | 39, male | Deterioration of work performance over 2 months | Multiple lesions in bilateral frontal white matter, corpus callosum, left lentiform nucleus, hypothalamus, pons | Prednisolone 60 mg/day, symptoms did not improve | Radiotherapy (whole brain, total 40Gy) effective for three months | Died of aspiration pneumonia three months after radiation therapy |
| Carlson (1996) | 76, female | Rapidly progressive encephalopathy with lethargy, confusion, disorientation, dysphasia | Bilateral cerebral white matter, thalami | Used | Steroids only | Died 1 month after dismissal |
| Furusawa et al. (1998) | 55, female | Tetraparesis, pseudo-bulbar palsy, akimic mutism over 4 months | Bilateral cerebral white matter and pyramidal tracts | Used | Chemotherapy (cisplatin), Radiotherapy (whole brain, total 24.8Gy) | Improved dramatically after oral steroids, chemo&radiation therapy |
| Bakshi et al. (1999) | 41, male | Forgetfulness, disorganization | Cerebral white matter with frontal predominance, corpus callosum, pons, cerebellum, and superior frontal gray matter | Intravenous methylprednisolone, 1 g daily, No improvement occurred | N | Died about 9 months after symptom onset |
| Bakshi et al. (1999) | 75, female | Rapidly progressive cognitive decline | Supratentorial paraventricular white matter | ND | ND | Died |
| Rollins et al. (2005) | 65, male | Memory loss, unstable gait | Bilateral cerebral hemispheres, corpus callosum, midbrain, periaqueductal region | ND | Chemotherapy (methotrexate) ineffective | Died 14 months after symptom onset |
| Rollins et al. (2005) | 80, female | Acute confusion | Bilateral cerebral white matter, pons, cerebral peduncles | ND | N | Died of pneumonia 5 weeks after acute confusion |
| Rollins et al. (2005) | 62, male | Acute confusional state, gait disturbance | An extensive deep white matter lesion involving the left periventricular areas, the caudate, internal and external capsule, thalamus, corpus callosum | Used, symptoms briefly improved | N | Died shortly after dismissal |
| Lewerenz et al. (2007) | 65, female | Insidious personality changes, forgetfulness, double vision | Bilateral frontal white matter, both putamina, caudate nuclei | Used, additionally with azathioprine. Symptoms disappeared in two weeks. | Chemotherapy (methotrexate) | Died 7 months after presentation |

Table 1 continued

| Author and year | Patient age (year), sex | Clinical presentations | Sites of involvement by MRI | Steroid administration (and response) | Treatment (Chemotherapy/radiation therapy) | Patient outcomes |
|-----------------|-------------------------|---------------------------------|--|---|--|---|
| Present case | 53, male | Unstable gait Disorientation | Bilateral cerebral white matter brain stem | Intravenous methylprednisolone, 1 g/day for 3 days, prednisolon Symptoms dramatically improved | Radiotherapy (whole brain, total 36Gy) | Clinically stable after 10 months after diagnosis |

ND: not described; N: none

Discussion

At presentation, PCNSL in immunocompetent patients almost always shows as single or multiple, nodular contrast-enhancing mass lesions within patchy T2-hyperintense areas on MRI [6]. Very rarely, the disease manifests as a diffuse, infiltrating form without a cohesive mass, a pattern called lymphomatosis cerebri [7, 8]. Because its clinical presentation and MRI findings mimic other white matter disorders, diagnostic problems often occur. It may go undiagnosed for prolonged periods of time thereby delaying treatment. In our case, the disease had been mistaken for demyelinating diseases such as multiple sclerosis, or degenerative disorders [11]. As is the case with ours, LC has been misdiagnosed as Binswanger’s disease (subcortical ischemic vascular dementia) [9, 11], infectious encephalomyelitis including progressive multifocal leukoencephalopathy (PML) [7, 9, 11, 13], toxic or metabolic abnormalities [11], unknown autoimmune diseases [10], or neoplasms like gliomatosis cerebri [9, 13].

Since the first description of LC by Bakshi et al. [7], several cases of LC have been reported into the literature [9, 10]. Retrospectively reviewed, before the introduction of the term LC by Bakshi et al. [7], several previous cases do exist, describing pathologically proven, primary CNS lymphomas which were nonenhancing on MRI [11–13] (Table 1). Some other cases with nonenhancing lesion on CT/MRI had been reported even previously [14, 15]. However, most of them were pathologically demonstrated after contrast enhancing mass appeared on MRI, or autopsy proven [7, 9–11, 15].

The present report is unique in that the course of disease progression was demonstrated by serial MRI which showed development of white matter changes thoroughly without contrast enhancement, and that was clinically consistent.

Diffuse white matter lesions without contrast enhancement in LC are pathologically supposed to be caused by widespread infiltration of white matter by lymphomatous cells [7, 9]. Lack of contrast enhancement on MRI is assumed to reflect intact blood-brain barrier (BBB), or it has been thought that significant BBB disruption by lymphoma cells is not yet produced [11, 12].

As well known, steroids can modify the enhancement pattern and cause resolution of PCNSL lesions [16]. In our case, although enhancing lesion was not detected, administration of steroids was cautiously withheld until biopsy, because those agents might clinically obscure the diseases’ development. Though spontaneous regression of lymphoma has been reported with systemic low grade lesions, there are few reported cases of spontaneous regression of PCNSL in which steroid administration was carefully ruled out as the cause of the improved clinical and imaging findings [17].

Although progression of the disease was rather sluggish in our case, patients usually deteriorate rapidly in the reported cases [7, 9–11]. To avoid deferring adequate treatment, biopsy is necessary to diagnose LC before clinical deterioration.

This report is also unique in that treatment was started before rapid clinical deterioration occurred. Though steroids were effective in some cases [9, 10, 13], they were not in the other [7, 11, 12]. Fortunately, steroid treatment dramatically ameliorated symptoms in this particular case, and he could be given whole brain irradiation in good condition. Remission has been obtained by radiotherapy alone for 10 months after diagnosis.

Acknowledgements We greatly appreciate Drs. Yoichi Nakazato and Atsushi Sasaki (Department of Human Pathology, Gunma University Graduate School of Medicine, Gunma, Japan) for providing specimens immunohistochemically stained for Iba-1 and CD68, and their valuable scientific support.

References

- Schwaighofer BW, Hesselink JR, Press GA et al (1989) Primary intracranial CNS lymphoma: MR manifestations. *AJNR Am J Neuroradiol* 10:725–729
- Poon T, Matoso I, Tchertkoff V et al (1989) CT features of primary cerebral lymphoma in AIDS and Non-AIDS patients. *J Comput Assist Tomogr* 13:6–9
- DeAngelis LM (1994) Primary central nervous system lymphoma. *Recent Results Cancer Res* 135:155–169
- Thurnher MM, Rieger A, Kleibl-Popov C et al (2001) Primary central nervous system lymphoma in AIDS: a wider spectrum of CT and MRI findings. *Neuroradiology* 43:29–35
- Buhring U, Herrlinger U, Krings T et al (2001) MRI features of primary central nervous system lymphomas at presentation. *Neurology* 57:393–396
- Kuker W, Nagele T, Korfel A et al (2005) Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. *J Neurooncol* 72:169–177
- Bakshi R, Mazziotta JC, Mischel PS et al (1999) Lymphomatosis cerebri presenting as a rapidly progressive dementia: clinical, neuroimaging and pathologic findings. *Dement Geriatr Cogn Disord* 10:152–157
- Kleihues P, Cavenee WK (eds) (2000) Pathology and genetics of tumours of the nervous system. International Agency for Research on Cancer (IARC) Press, Lyon
- Rollins KE, Kleinschmidt-DeMasters BK, Corboy JR et al (2005) Lymphomatosis cerebri as a cause of white matter dementia. *Hum Pathol* 36:282–290
- Lewerenz J, Ding X, Matschke J et al (2007) Dementia and leukoencephalopathy due to lymphomatosis cerebri. *J Neurol Neurosurg Psychiatry* 78:777–778
- Terae S, Ogata A (1996) Nonenhancing primary central nervous system lymphoma. *Neuroradiology* 38:34–37
- Carlson BA (1996) Rapidly progressive dementia caused by nonenhancing primary lymphoma of the central nervous system. *AJNR Am J Neuroradiol* 17:1695–1697
- Furusawa T, Okamoto K, Ito J et al (1998) Primary central nervous system lymphoma presenting as diffuse cerebral infiltration. *Radiat Med* 16:137–140
- DeAngelis LM (1993) Cerebral lymphoma presenting as a non-enhancing lesion on computed tomographic/magnetic resonance scan. *Ann Neurol* 33:308–311
- Matsumoto K, Kohmura E, Fujita T et al (1995) Recurrent primary central nervous system lymphoma mimicking neurodegenerative disease—an autopsy case report. *Neurol Med Chir (Tokyo)* 35:360–363
- Vaquero J, Martinez R, Rossi E et al (1984) Primary cerebral lymphoma: the “ghost tumor”. *J Neurosurg* 60:174–176
- Partap S, Spence AM (2006) Spontaneously relapsing and remitting primary CNS lymphoma in an immunocompetent 45-year-old man. *J Neurooncol* 80:305–307