

SHORT REPORT

## Case report of unusual leukoencephalopathy preceding primary CNS lymphoma

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### Abstract

**A previously healthy 35 year old woman presented with bilateral uveitis associated with multiple, evolving, non-enhancing white matter lesions consistent with a progressive leukoencephalopathy such as multiple sclerosis. Thirty months after her initial presentation, she was diagnosed with primary CNS lymphoma and died 14 months later. The unusual clinical course preceding the diagnosis suggests that a demyelinating disease may have preceded, and possibly heralded, the development of primary CNS lymphoma. Cases of "sentinel lesions" heralding the diagnosis of primary CNS lymphoma have been reported, and this case further corroborates such instances and raises further issues regarding possible neoplastic transformation occurring in inflammatory diseases such as multiple sclerosis.**

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Primary CNS lymphoma is a rare malignant tumour comprising less than 1% of all primary brain tumours, but the incidence of which has increased threefold in the last decade in immunocompetent patients.<sup>1</sup> Although the disease commonly presents with mental status changes, headache, or seizures<sup>2</sup> in the setting of enhancing, periventricular, steroid sensitive masses, others have reported antecedent or heralding neurological symptoms associated with infections such as Lyme disease<sup>3</sup> and immunodepressive states such as AIDS<sup>4</sup> and chronic immunosuppression.<sup>5</sup> Rarely, cases of primary CNS lymphoma have initially coincided with features of demyelinating disease.<sup>6-12</sup> Recently, Alderson *et al* reported four patients with "sentinel lesions" simulating multiple sclerosis that heralded the subsequent diagnosis of primary CNS lymphoma within 7 to 11 months.<sup>6</sup>

We report a patient in whom primary CNS lymphoma was confirmed by biopsy and post-mortem examination but whose clinical and radiological disorder was most likely a progressive leukoencephalopathy.

### Case report

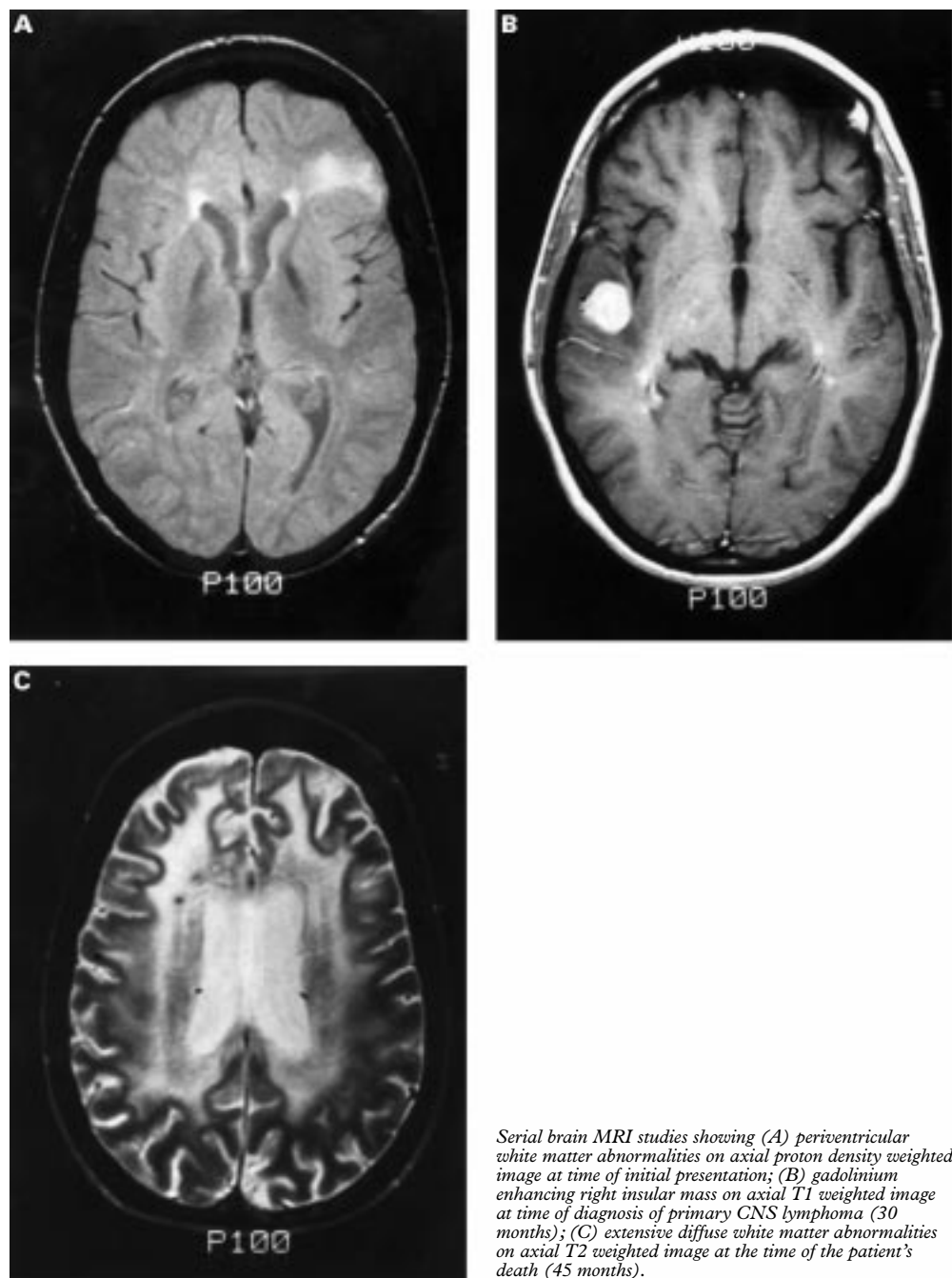
A previously healthy 35 year old left handed woman developed blurred vision of her right eye and was diagnosed with uveitis. Despite treatment with intraocular corticosteroid injections, the uveitis persisted and, by the next spring, involved her left eye. She underwent a brief course of cyclosporin treatment without effect. Multiple ocular cytologies failed to disclose malignant cells and a diagnosis of pars planitis was made. About 1 year after the onset of her blurred vision, she developed extreme fatigue, numbness of her hands, dizziness, myalgias, and frequent headaches. Brain MR showed numerous white matter foci of T2 signal hyperintensity without enhancement (figure A). The pattern shift visual evoked response was prolonged in the right eye. Lyme titre was equivocal with a titre of 14.9. Lumbar CSF contained 6 white blood cells/mm<sup>3</sup>, of which 95% were lymphocytes and 5% monocytes; the concentrations of protein (36 mg%) and glucose (53mg%) were normal. Oligoclonal bands were not present. Myelin basic protein was <0.5. Lyme titre in CSF was 2.17. She underwent a 30 day course of doxycycline for possible neuro-Lyme disease with transient benefit. Eight months after the first MRI and treatment with doxycycline, brain MR showed extended periventricular white matter lesions with a prominent lesion in the white matter of the frontal lobes involving the corpus callosum. A diagnosis of multiple sclerosis was considered. Nine months later and 24 months after her initial presentation, MRI showed persistent T2 periventricular white matter abnormalities with enhancement in the regions of the left temporal lobe and subcortical white matter. Generalised seizures developed at 30 months at which time the brain MR showed a new 2x2 cm, gadolinium enhancing T1 nodule with surrounding oedema in the right insula (figure B). A large cell malignant lymphoma was identified on biopsy. The surrounding white matter was not sampled. One month later, she was given the first of seven cycles of chemotherapy with methotrexate, cyclophosphamide, vincristine, adriamycin, and dexamethasone. Six months later, 1 month after completing her seventh cycle of chemotherapy, she was admitted to hospital when generalised seizures were followed by left hemiparesis and left homonymous hemianopia. After whole brain irradiation

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Serial brain MRI studies showing (A) periventricular white matter abnormalities on axial proton density weighted image at time of initial presentation; (B) gadolinium enhancing right insular mass on axial T1 weighted image at time of diagnosis of primary CNS lymphoma (30 months); (C) extensive diffuse white matter abnormalities on axial T2 weighted image at the time of the patient's death (45 months).

(50 Gy in 1.2 Gy fractions provided 4 months after chemotherapy) brain MRI showed enhancing lesions of smaller size with persistent periventricular T2 abnormalities. She was readmitted to hospital the subsequent month with worsening of her left hemiparesis, new right hemiparesis, persistent global headache, and lethargy. Brain MRI showed extensive T2 hyperintensity of nearly the entire white matter without enhancement (figure C). Magnetic resonance imaging of the cervical and thoracic spine showed intramedullary oedema and linear enhancement from C2 through C4 and from C5 through T2. Brain biopsy of deep white matter 1 month later showed cerebral tissue with gliosis, perivascular lymphocytes, and microglial infiltration without evidence of

malignancy. An HIV test was negative. She continued to decline with persistent seizure activity and progression of her weakness to tetraplegia. Brain MRI 1 month later showed diffuse T2 bright signal without enhancement involving nearly all visualised intracerebral white matter with relative sparing of the deep and cortical grey matter, unchanged from the previous study. She died 45 months after the onset of her initial symptoms and 14 months after her first brain biopsy disclosed malignant lymphoma.

Necropsy limited to the brain (weight 1200 g) showed extensive infiltration of the brain from the leptomeninges and outer grey matter of the cerebral cortex to the upper cervical spinal cord by large, round, discohesive tumour

cells measuring 13–15 µm in diameter with vesicular nuclei containing coarse chromatin and often a single, prominent nucleolus, consistent with the tumour found on the first brain biopsy. The cortical white matter was severely demyelinated, rarefied, and gliotic with occasional foci showing confluent near total demyelination with axonal preservation, blurry borders, spared U fibres, and moderate tumorous infiltration. Occasional vessels were occluded by masses of tumour cells extending centrifugally through their walls and spilling into the surrounding parenchyma. Immunohistochemistry showed diffuse staining of tumour cells with CD26 consistent with malignant B cell lymphoma. Examination of the posterior pole of the right eye, extraocular muscles, and peroneal and optic nerves demonstrated no involvement by tumour.

DNA extracted from deparaffinised sections (40 mm thick) of cerebral tissue containing foci of malignant lymphoma using the QIAamp Tissue kit (Qiagen, Inc, Chatsworth, CA, USA) were subjected to nested polymerase chain reaction (PCR) amplification using primer pairs to detect the Epstein-Barr virus genome<sup>13</sup> and b-actin (positive control). The PCR products were fractionated by electrophoresis and analysed by Southern blot hybridisation using oligonucleotide probes corresponding to internal sequences of the Epstein-Barr virus amplified product.<sup>13</sup> The results of three separate experiments showed no detectable Epstein-Barr virus genome in CNS tissues, although b-actin gene sequences (9420 bp PCR product) were readily amplified, and positive control studies of Epstein-Barr virus immunoreactive lymphomas yielded the expected 209 bp PCR product.

### Discussion

A previously healthy 35 year old woman presented with bilateral uveitis associated with multiple, non-enhancing white matter lesions, developed additional enhancing lesions and, 30 months after initial presentation, was diagnosed with primary CNS lymphoma. A disease process characterised by multiple, non-enhancing white matter lesions consistent with demyelinating disease preceded, and may have heralded, the diagnosis of primary CNS lymphoma.

The usual interval from initial presentation to diagnosis of primary CNS lymphoma is about 3 months.<sup>2</sup> Although the prolonged duration of symptoms of 30 months in this patient is not unprecedented, it is not typical. In a series of 64 patients with primary CNS lymphoma, O'Neill and Illig reported that 8% had symptom durations of 24 to 104 weeks.<sup>2</sup> Additional studies have reported sporadic patients with prolonged duration of symptoms, the most protracted of which were 4<sup>14</sup> and 5<sup>15</sup> years. Of particular interest are the cases reported by Schaumberg *et al*,<sup>11</sup> Williams *et al*,<sup>12</sup> and Ruff *et al*,<sup>16</sup> in which relapsing and remitting signs and symptoms resembling multiple sclerosis were followed up to 8 years later by a fulminant terminal course of primary CNS lymphoma.

Despite postmortem examination, we cannot provide a definitive diagnosis for the evolving multifocal leukoencephalopathy preceding the diagnosis of primary CNS lymphoma in this patient. Although foci of near total demyelination with axonal preservation involving cortical white matter were present, these areas showed tumour infiltration and radiation effect and cannot be definitely shown to represent plaques of multiple sclerosis. The chief diagnostic considerations were multiple sclerosis/acute disseminated encephalomyelitis and infectious encephalitis such as neuro-Lyme disease or HIV encephalopathy; HIV encephalopathy was considered unlikely because the patient had no clinical evidence of immunodeficiency, including HIV infection. The demyelination changes were thought to be excessive for radiation alone, and more profound than those previously associated with the combination of chemotherapy followed by cranial irradiation.

Lyme disease and progressive multifocal leukoencephalopathy have been reported in association with primary CNS lymphoma.<sup>3,17</sup> Common to these entities are enhanced lymphocytic proliferation incited by an infectious agent culminating in neoplasia.<sup>18</sup> In particular, multiple sclerosis has been linked with primary CNS lymphoma. A possible epidemiological association between multiple sclerosis and lymphoma/leukaemia has been reported<sup>19</sup> and three cases of coincident primary CNS lymphoma and multiple sclerosis have been documented in the world literature.<sup>7,8,10</sup> Gherardi *et al*, in their report on a 24 year old man with coexistent primary CNS lymphoma and multiple sclerosis, suggested that the association may be more than coincidental.<sup>10</sup>

Cases of lymphoproliferative disease with transition from polyclonal to monoclonal B cell proliferation have been reported in association with infectious mononucleosis and chronic immunosuppression. Hanto *et al* have hypothesised that polyclonal B cell proliferations may evolve into monoclonal tumours with greater potential for malignant growth.<sup>20</sup> Epstein-Barr virus has been implicated as a transformative agent in this evolution. The association of primary CNS lymphoma with congenital or acquired immunodeficiency conditions is well documented<sup>18</sup> and implicates immune system predisposition<sup>4</sup> to reactivation of Epstein-Barr virus infection. Epstein-Barr virus implicated in the pathogenesis of primary CNS lymphoma in immunocompetent patients is less constant. Although the Epstein-Barr virus is not causative here, as shown by our negative PCR studies for the Epstein-Barr virus genome, our patient and those reported by Alderson *et al* in which "sentinel lesions" preceded diagnostic biopsies of primary CNS lymphoma by 7 to 11 months<sup>6</sup> suggest a common pathogenic mechanism for both the prodrome and primary CNS lymphoma. The present case and those of Alderson *et al* raise the possibility that lymphocytic infiltrates which accompany leukoencephalopathy may undergo transformation to malignant B cell populations.

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