Cerebral lymphoma presenting as a leukoencephalopathy

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Abstract

Cerebral lymphoma is frequent in immunocompetent patients. This tumour usually appears on CT and MRI as a single lesion or as multiple lesions with mass effect and homogeneous enhancement after contrast administration. A patient is described with a cerebral lymphoma, confirmed by histopathological examination, who presented as a progressive leukoencephalopathy.

Keywords: cerebral lymphoma; computed tomography; leukoencephalopathy; magnetic resonance imaging

Primary lymphoma of the CNS represents 1%-2% of intracranial tumours and about 1% of non-Hodgkin’s lymphomas. It is usually associated with acquired immunodeficiency syndrome (AIDS)—1.9%-6% of patients with AIDS develop CNS lymphoma—or with other causes of long term immunosuppression (transplants, congenital immunological deficiencies, etc). In the past few years, the incidence of primary CNS lymphoma in immunocompetent patients has increased threefold.

In 90% of cases, cerebral lymphoma is identified as single or multiple lesions with mass effect and homogeneous enhancement after contrast administration, both on CT and on MRI. Radiological findings may suggest the diagnosis before histopathological confirmation. Metastases in the CNS from systemic lymphoma show similar radiological findings.

The presentation of cerebral lymphoma as a diffuse leukoencephalopathy is not frequent and can be confused with other neurological diseases. We report on a patient with cerebral lymphoma presenting as a progressive leukoencephalopathy.

Case report

A 58 year old woman was admitted to hospital on November 1998 because of four months of progressive gait instability, paraesthesias in the right face, intermittent horizontal diplopia and difficulty in speaking. Neurological examination showed bilateral pyramidal signs, ataxic gait, and dysarthria. Laboratory studies, including blood cell count, a coagulation study, routine serum biochemistry, serum concentrations of vitamin B12, folic acid, immunoglobulins, C3, C4, antinuclear antibodies, rheumatoid factor, serum and urine electrophoresis, and plasma and 24 hour urine cortisol concentrations, were all normal or negative. Analysis of CSF showed 8 cells/mm³ (mononuclear), protein concentration 52 mg/dl, and glucose 50 mg/dl (blood glucose 92 mg/dl); there was no intrathecal synthesis of IgG nor oligoclonal bands, and cytological analysis was negative. Plasma concentrations of very long chain fatty acids and leucocyte arylsulphatase activity were normal. Serological studies for neurotropic viruses (including Epstein-Barr and human immunodeficiency viruses), Borrelia burgdorferi, Brucella sp, and syphilis were negative, both in the serum and in the CSF. A chest radiograph and a cranial CT were normal. Brain MRI without contrast showed scattered confluent lesions affecting the white matter of both hemispheres, the splenium of the corpus callosum, cerebellum, and brain stem.

In February 1999, the neurological situation worsened. In addition to the previous symptoms, speech became unintelligible because of severe dysarthria (comprehension and elaboration remained adequate); and there was dysphagia for liquids and solids, diplopia, bilateral manipulative clumsiness, and difficulty in walking, due to instability. Examination showed severe dysarthria, bilateral impairment of upper vertical and lateral gaze without ophthalmoplegia, flaccid tetraparesis (4/5 in upper limbs and 2/5 in lower limbs) with generalised hyperreflexia, flexor plantar responses, and severe gait ataxia. A new cranial MRI showed worsening of the previous white matter lesions (fig 1 D, E, and F) which showed no pathological enhancement with gadolinium.

An open brain biopsy obtained from the right frontal lobe was macroscopically normal. Light microscopy showed atypical lymphoid proliferation with an angiocentric infiltration...
pattern, and infiltration of the parenchyma from perivascular spaces (fig 2 A). The atypical lymphoid cells had a large nucleus with dispersed chromatin, and sometimes prominent nucleoli and scarce cytoplasm (fig 2 B). The lymphoid proliferation showed a diffuse growing pattern, with focal leptomeningeal involvement, moderate infiltration of the brain cortex, and marked infiltration of the white matter, together with diffuse demyelination. Tumorous cells showed immunoreactivity to B-cell markers (CD20, CD45, and CD79a). In addition, some cells were immunoreactive for T cell markers (CD4 and CD3). The cellular proliferation index marked with Ki-67 was 32%. In conclusion, the histopathological diagnosis was high grade lymphoma with an immunohistochemical phenotype of diffuse large B cell lymphoma.

After surgery, the patient had progressive neurological worsening, and developed an aspirative pneumonia which needed orotracheal intubation and later tracheostomy. Treatment with cytarabine was started, but the patient died 4 days later. The family denied necropsy.

Discussion
Our patient presented with symptoms suggesting multifocal involvement of the CNS. Brain MRI showed scattered and confluent white matter lesions without contrast enhancement, which were diagnosed as lymphoma on biopsy. The clinical presentation and the radiological features are unusual.8–10

Figure 1  (A, B, and C) November 1998. T2 weighted (TR 2500 ms, TE 100 ms) axial MRI demonstrating widespread increased signal areas in the white matter in several locations. (A) At infratentorial level in the right median pedunculum cerebellum and pons. (B and C) Multiple lesions in brain hemispheres, posterior limb of the internal capsule, splenium of the corpus callosum, and occipital and frontal lobes. They have no mass effect and do not involve grey matter. (D–F) February 1999. Control evolution. T2 weighted (TR 2500 ms, TE 100 ms) axial MRI images that show a larger extension of the white matter lesions, mostly in the right hemisphere. The grey matter was not involved (D and E). T1 weighted axial MRI (TR 400 ms, TE 22 ms) with gadolinium (F) does not show pathological enhancement.
In immunocompetent patients, cerebral lymphoma usually occurs during the 6th and 7th decades of the life,\textsuperscript{11} and presents with focal findings or evidence of raised intracranial pressure.\textsuperscript{12} From the histopathological point of view, cerebral lymphoma is usually a monoclonal type B lymphoma of intermediate or high degree of malignancy, and is characterised by rapid growth, limited to the CNS.\textsuperscript{13} Five year survival approaches 4%,\textsuperscript{14} and the course without any treatment is rapidly fatal, with a mean survival of 3 months.\textsuperscript{15} In our patient, the course was rather more prolonged, and the evolution was similar to that of a progressive leukoencephalopathy. Although steroids may produce a significant decrease in tumour burden,\textsuperscript{16} 17 our patient did not improve with these drugs.

In 75%–85% of cases, lymphomas are located at a supratentorial level. They usually present as single or multiple lesions of central location, mainly in the basal ganglia, the periventricular region, and the corpus callosum.\textsuperscript{18}

On CT, cerebral lymphomas are isodense or slightly hyperdense with a mild mass effect, and show an intense and homogeneous enhancement after contrast administration.\textsuperscript{3} On MRI they are isointense or slightly hypointense in relation to the white matter in T1 weighted images, and they are isointense or slightly hyperintense in T2 weighted images.\textsuperscript{3} About 75% out of all cases in immunocompetent patients show an intense and homogeneous marked enhancement after contrast administration.\textsuperscript{18} In immunodepressed patients the presence of necrosis, which appears as ring enhancement, is frequent.\textsuperscript{19}

Because of the presence of a diffuse leukoencephalopathy on the MRI of our patient we used various diagnostic tools to exclude inflammatory demyelinating diseases such as multiple sclerosis, metabolic diseases such as adrenoleukodystrophy, infectious diseases (Lyme disease, progressive multifocal leukoencephalopathy, AIDS, etc), or gliomatosis cerebri. The predominant demyelination in this case might be explained in different ways. As some cases have been reported of demyelinating neurological diseases preceding or linked to lymphomas,\textsuperscript{20–24} a common pathogenesis is possible: the lymphocytic infiltrate seen with the leukoencephalopathy might degenerate towards a malignant cell population. On the other hand, demyelination could be associated with lymphoma.

The absence of contrast enhancement is unusual and may suggest a partial preservation of the blood-brain barrier.\textsuperscript{7} Although the absence of contrast enhancement in the second study of our patient could be a result of treatment with corticosteroids,\textsuperscript{3} the absence of enhanced image during the first MRI does not support this hypothesis.

Despite its rarity, we must bear in mind the diagnosis of cerebral lymphoma in the presence of neurological diseases affecting mainly the white matter on neuroimaging studies.

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\textsuperscript{8} De Angelis L. Cerebral lymphoma presenting as a non-enhancing lesion on computed tomographic/magnetic resonance scan. Am J Neurol 1993;145:508–11.

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