PostScript

LETTERS

Remission of progressive multifocal leucoencephalopathy in SLE after treatment with cidofovir: a 4 year follow up

Progressive multifocal leucoencephalopathy (PML) is an opportunistic infection caused by human polyomaviruses such as the JC virus. It usually occurs as a severe complication of immunosuppression in patients with primary disorders of the immune system or secondary impairment of immune function, for example, after iatrogenic states of immunosuppression. PML usually takes a rapidly progressive course and advances to death within 1 to 18 months. Today, PML is mainly seen in AIDS, while previously it was typically found in patients with granulomatous, neoplastic, or infectious diseases. In granulomatous diseases particularly, PML is thought to occur as a result of iatrogenic states of immunosuppression, but it is also seen in patients aggressively treated with immunosuppressive agents for systemic lupus erythematosus (SLE).[1 2] PML progresses to death in most of these patients even after withdrawing immunosuppressive therapy.[2] Therefore additional therapy, aimed at supporting a more rapid restoration of immune function his warranted.

Case report

We report a 40 year old woman diagnosed with SLE at the age of 20 years, based on four American College of Rheumatology criteria (erythema, arthritis, elevated antinuclear antibodies, and anti-dsDNA antibodies). Owing to neuropsychiatric lupus (the patient had experienced several psychotic episodes) with suspected vasculitic changes on cerebral magnetic resonance imaging (MRI), the patient had undergone 12 cycles of cyclophosphamide pulse therapy in 1995/96 followed by immunosuppressive treatment with mycophenolate mofetil in 1998, and azathioprine in 1999. Follow up cerebral MRI scans at that time were normal.

In January 2001, she again developed psychotic episodes and an initially mild ataxia. She had repeatedly been put on low doses of corticoids but on no other immunosuppressive therapy during the previous 2 years. MRI revealed a lesion in the left cerebellum, which was hyperintense on T_2 and hypointense on T_1 weighted images. No lesions were seen in the cerebral hemispheres. Central nervous system manifestation of SLE was suspected, although the patient revealed only moderate signs of SLE activity (elevated anti-dsDNA antibodies, slightly decreased complement levels C3c and C4, increased erythrocyte sedimentation rate, but normal C reactive protein). There were no signs of severe immunosuppression; laboratory data showed normal levels of immunoglobulins and only slightly decreased lymphocytes, especially CD8+ T lymphocytes. The patient received two pulses of cyclophosphamide and high doses of corticosteroids to reduce the presumed cerebral SLE activity. In addition, she received antipsychotic medication.

While the psychosis was readily controlled by this treatment, the patient deteriorated neurologically. She developed a severe, disabling, rapidly progressive, left sided hemiataxia. and was unable to walk. A control MRI of the brain in February 2001 revealed a progression of the lesion in the left cerebellum and a new lesion in the middle cerebellar peduncle. The lesions again presented as hyperintense on T_2 and hypointense on T_1-weighted images (fig 1A). Owing to the neurological deterioration after initiation of immunosuppression and the presentation of the lesions on MRI, PML was considered as a differential diagnosis. PCR revealed JC virus DNA in the cerebrospinal fluid (CSF). As cerebral SLE and PML require an intense but divergent therapy, a brain biopsy was obtained from the cerebellar lesion. Histopathology confirmed the diagnosis of PML. HIV tests were negative, T cell counts were normal, and signs of malignancy were lacking. Immunosuppression was discontinued. Because PML is usually lethal in patients with SLE even after omission of immunosuppression,[1 2] we considered options for an active antiviral therapy. There was evidence from several reports in AIDS patients that cidofovir, an inhibitor of viral DNA polymerase, may reduce the size of PML lesions and thus prolong survival.[3 4] Lacking therapeutic alternatives we therefore administered intravenous cidofovir (5 mg/kg body weight) at initially bi-weekly intervals, after obtaining informed consent. After the third and fourth cycle, the patient improved dramatically. She was able to walk again and only showed a mild residual ataxia. MRI revealed reduction of the lesions in the cerebellum and middle cerebellar peduncle with no new sites of active disease (fig 1B). PCR for JC virus DNA in the CSF was now negative. The treatment with cidofovir was continued with longer intervals (8–12 weeks). The therapy was generally well tolerated. After the fifth cycle, mildly increased creatinine levels were found. After one cycle with 4 mg cidofovir/kg body weight, kidney function was quickly normalised and the following cycles could be administered at the initial dosage. Fourteen months after initiation of the treatment, the patient had completed the 10th cycle of therapy with no signs of disease activity. MRI scans of the brain showed further regression of the lesion with no signs of

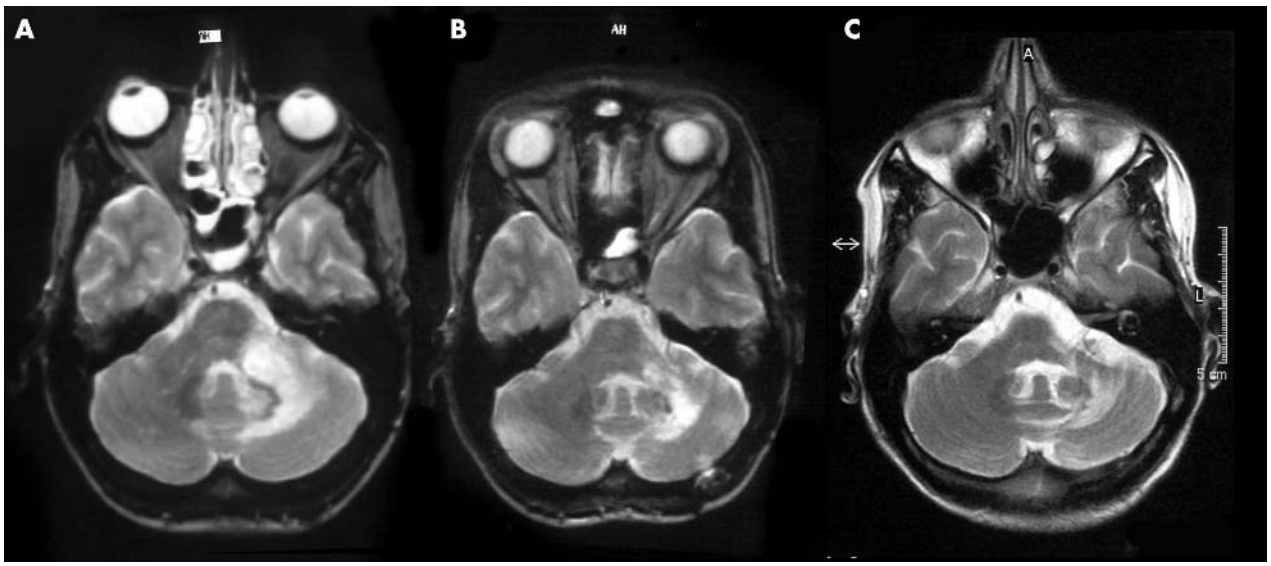

Figure 1 T2 weighted MRIs showed (A) extended white matter lesions in the middle cerebellar peduncle and left cerebellum, February 2001; (B) regression of the lesions after four cycles of cidofovir, July 2001; and (C) further regression with residual gliotic lesions, July 2004.

active inflammation (not shown), and cidofovir treatment was discontinued. At present, (4 years follow up after the first treatment and 2.5 years after the last cycle of cidofovir), the patient still shows no signs of disease activity. CSF PCR for JC virus DNA remains negative, and a recent MRI scan of the brain was unchanged (fig 1C). As of March 2005, the patient lives at home, is able to walk, and is independent.

Discussion

We report a patient with SLE who survived PML after treatment with cidofovir and discontinuation of immunosuppression. First evidence for possible efficacy of cidofovir in the treatment of PML in a patient with SLE was presented in a case report.[5] Discontinuation of immunosuppression and treatment with cidofovir resulted in reversal of JC virus positivity and stabilisation of MRI lesions. However, the patient died due to serious kidney failure.

It remains unclear whether the improvement in both patients was induced or supported by cidofovir or whether it could have been acquired by discontinuation of immunosuppression alone. However, patients with PML in SLE usually die after discontinuation of immunosuppression alone.[1 2] Interestingly, our patient did not show signs of severe immunosuppression at the point of manifestation of PML. These observations may suggest a predisposition of patients with SLE to PML that may not be explained by their immunosuppression alone.

We conclude that cidofovir should be offered to SLE patients developing PML due to immunosuppression in addition to withdrawal of immunosuppressive therapy, as death is likely without antiviral therapy. Cidofovir may be effective against PML caused by non-AIDS related states of immunosuppression.

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Dramatic improvement in non-AIDS related progressive multifocal leucoencephalopathy

Progressive multifocal leucoencephalopathy (PML) is a rare disorder occurring when a strain of papovavirus (JC virus) infects the central nervous system. It results in a generally quick and fatal outcome. It is associated with cell mediated immune deficient diseases but some few cases were reported in immunocompetent hosts. Since 1981, it has been commonly associated with AIDS. In AIDS related PML, long term survival without real neurological improvement has been reported in patients treated with highly active antiretroviral therapy (HAART).[1] Few cases of improvement with cidofovir or cytosine arabinoside have been described in AIDS related or non-AIDS-related PML,[2 3] but in larger trials in AIDS related PML, no clinical benefit was found.[4] As a whole, the treatment of this progressive demyelinating disease remains controversial, in particular in the rare cases of non-AIDS-related PML. We describe a patient with an underlying haematological disease, without clear cut immune cell deficiency, who developed rapidly progressive PML. The patient showed clinical, virological, and imaging improvement when treated with an association of intravenous and intrathecal cytosine arabinoside combined with intravenous cidofovir.

A 48 year old man presented with progressive multiple lymphadenopathies, hepatosplenomegaly, weight loss, and blood cell count abnormalities. Fine needle aspiration cytology of lymphadenopathy diagnosed marginal zone B cell lymphoma. There was also bone marrow and blood proliferation. A few weeks after the diagnosis, the patient noticed rotatory vertigo and visual problems suggestive of a right homonymous hemianopia. Because of dissemination and the large tumour mass, chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone) was started one month after the onset of neurological symptoms. Following the first course of chemotherapy, his neurological symptoms worsened, and language disorders appeared. No real immunodeficiency was shown—the absolute CD4+ count was 549/mm^3 (normal 858±260), and there was discrete hypogammaglobulinaemia (4.6 g/l; normal 5–12). The patient was HIV and HTLV1 seronegative. Cerebral magnetic resonance imaging showed a non-contrast-enhancing lesion in the left occipital white matter (fig 1A).

Cerebrospinal fluid (CSF) analysis was normal apart from a moderate increase in CSF protein (0.7 g/l). Suspicion of PML was confirmed by a positive polymerase chain reaction (PCR) for JC virus DNA. Chemotherapy was discontinued (after one cycle) but neurological symptoms worsened rapidly and the patient developed a right hemiplegia, global aphasia, alexia and agraphia, apraxia, and cortical blindness concurrently with MRI deterioration (fig 1B).

Three months after his first symptoms, treatment was started with intravenous aracytine 2 mg/kg/d for five days every three weeks, combined with intrathecal aracytine (30 mg) weekly and intravenous cidofovir 5 mg/kg/d once every two weeks. The main adverse effect of this treatment was grade IV bone marrow toxicity, inducing spacing in the rhythm of treatment administration. One week after treatment onset, the patient stabilised and after one month began improving. After three months, he had recovered completely from his hemiplegia, and had significant improvement in his aphasia and cortical blindness. Right hemianopia and minor alexia without agraphia persisted. This dramatic improvement was confirmed by cerebral imaging, by the absence of JC virus DNA detection in CSF, and by a specific response of CD4+ T cells against JC virus. We decided to continue subcutaneous aracytine 2 mg/kg/d for five days monthly and intravenous cidofovir twice weekly. Fifteen months after treatment onset, the patient was ambulatory and cerebral MRI continued to improve (fig 1C). Lymphoma tumour burden did not clearly change during the treatment.

Comment

We report the favourable outcome of a patient with non-AIDS-related PML treated with a combination of intravenous and intrathecal aracytine and cidofovir. As the patient was not immunocompromised and had not received immunosuppressive treatment at PML onset, risk factors for the occurrence of PML are unclear. Treatment led to a rapid clinical and radiological improvement which was long lasting despite treatment delay and the patient's worrying clinical condition at treatment onset. Dose and administration schedules of cytarabine and cidofovir were derived from reports suggesting individual beneficial effects of these drugs.[2 3] To our knowledge, these drugs have not been used in combination before. In comparison with previous reports, the present case suggests a more rapid and prolonged effect of this therapeutic combination than with either aracytine or cidofovir treatment alone. This efficacy may be explained by a synergy between the drugs and by their different routes of administration. We thought that the improvement in our patient was related to the treatment because there was a temporal link with treatment onset and because of the radiological features (the rare cases of PML stabilising without specific treatment have usually been associated with an inflammatory response to the virus, indicated by contrast enhancement on imaging).

The main limiting factor of this treatment was bone marrow toxicity. During the periods of immune deficiency, the patient's neurological condition did not deteriorate, suggesting that PML occurrence in this patient was linked to a qualitative defect of CD4 cells rather than to their absolute count. Immunological studies have shown that JCV specific CD4-T cell responses play a