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Abstract

Background To report the clinical course of PML in an immunocompetent patient treated with cidofovir

Methods An immunocompetent 35-year-old man who developed progressive hemianopsia, aphasia, and limb weakness underwent repeated MRI scan of the brain, spinal fluid analyses, and brain biopsy.

Results Before diagnosis was established based on brain biopsy he was consecutively treated with methylprednisolon, acyclovir, ceftriaxon and plasmapheresis, but deteriorated rapidly suggestive of the immune reconstitution inflammatory syndrome (IRIS). He started to recover two weeks after initiation of treatment with cidofovir and has three years later suffered no relapse. MRI has shown marked improvement.

Conclusion PML should be considered in immunocompetent patients with typical clinical course and MRI findings. Treatment with cidofovir should be considered as early in the disease course as possible.
Backgrounds

Progressive multifocal leukoencephalopathy (PML) which is caused by the JC virus (JCV), is a rare and usually fatal demyelinating disease of the central nervous system typically occurring in severely immunosuppressed patients. The diagnosis of PML is presumptive when based on clinical or radiological evidence and the detection of JCV DNA in cerebrospinal fluid (CSF) by means of the polymerase chain reaction (PCR). The diagnosis is definitive by detection of viral protein or DNA by immunohistochemistry or in situ hybridisation of brain biopsies, respectively. While the JCV genomes of urine isolates usually have an archetypal regulatory region, genomes detected in CSF and brains from PML patients always have a rearranged viral regulatory region. Even though the majority of PML cases are found in HIV infected patients, cases have been diagnosed in patients with other cellular immunodeficiencies due to haematological malignancy, chemotherapy, organ transplantation, lymphocyte depletion as well as systemic lupus erythematosus. Increasing numbers of PML in patients exposed to monoclonal antibody therapy such as natalizumab, rituximab, and efalizumab have been reported.

PML is often fatal, but prolonged survival has been reported during antiviral treatment of cidofovir. No definitive guidelines for treatment of PML have been established. The treatment is often complicated by the immune reconstitution inflammatory syndrome (IRIS). Here, we report an immunocompetent man with PML probably complicated with IRIS who was successfully treated with cidofovir.
Case presentation

A 35-years-old man was admitted to the Department of Neurology, Haukeland University Hospital in Bergen, Norway because of increasing reading problems during the last four weeks. Apart from surgery for appendicitis 16 years earlier the patient was previously healthy. On admission, the neurological examination was normal except for a bilateral lower right-sided quadrant anopsia.

Magnetic resonance imaging (MRI) showed occipital white matter lesions mainly on the left side (Figure 1 A). CSF analyses were normal (PCR on JCV was not performed). Extensive haematiological and immunological blood analyses were performed including electrolytes, creatinine, liver enzymes, and CRP and they were all normal. The patient remained HIV negative on repeated tests.

Ten days after admission the patient had developed a complete bilateral right-sided hemianopsia and slight bilateral left-sided quadrant anopsia. New MRI showed progression of the white matter lesions (Figure 1 B). The patient was consecutively treated with high dose methylprednisolon, acyclovir, ceftriaxon and plasmapheresis. However, the vision disturbances progressed and in addition he developed aphasia and paresis of the right arm. Four weeks after admission brain biopsy was taken from the left occipital lobe lesion. Histology showed demyelinisation and atypical astrocytes suggestive of PML (Figure 2 A-D). PCR performed on extracted DNA from brain biopsy specimens was strongly positive for JCV. Retrospective quantitative PCR analysis of the original CSF was performed \(^{12}\) and showed 2500 JCV genome copies/ml. Sequencing analysis of the JCV genome \(^{13}\) showed a highly rearranged unique non-coding control region denoted PML HL (Figure 3). Retrospective enzyme immunoassay serum analysis (EIA)\(^{13}\) showed JCV IgG antibodies at the time of
hospitalization and the titers gradually increased at the 3-month follow-up. However, the JCV IgM levels were low and constant (Figure 4).

Treatment with intravenous cidofovir was initiated five weeks after admission. The patient received 350mg once a week for three weeks and thereafter every fortnight for 6 months. Two weeks after onset of treatment with cidofovir the patient reported some improvement of the paresis in his right arm but the MRI (Figure 1 C) performed after 3 ½ weeks treatment showed further progression compared with the MRI performed 2 weeks before onset of treatment with cidofovir. However, the patient continued to improve clinically, and he recovered completely from the paresis of the right arm and the aphasia. After two months treatment he also reported slight improvement of his vision.

MRI performed after 4 months treatment showed marked regression of white matter lesions. The patient’s vision improved slightly during the next months, and the MRI (Figure 1 D) showed further improvement after 6 months. White matter lesions remained unaltered on further MRI investigations, the last one being performed 30 months after onset of treatment with cidofovir. Follow-up PCR analysis of the CSF seven months after onset of treatment with cidofovir was JCV negative.

The patient developed epilepsy 9 months after onset of symptoms.

Comprehensive investigations including antinuclear antibodies, quantification of immunoglobulins, electrophoresis, CD4- and CD8 counts as well as complement (C3,C4) were all normal, except for moderate reduced levels of IgA (0.55 g/L).

On the last follow-up 36 months after onset of treatment with cidofovir the patient had suffered no relapse.
Conclusion

This case report of PML highlights several interesting points. Firstly, immunocompetent persons may develop PML, and secondly, treatment with cidofovir may be successful. Thirdly, the increased progression of symptoms after initiating antiviral and antibiotic therapy, methylprednisolone and plasmapheresis, was suggestive of immune reconstitution inflammatory syndrome (IRIS). This complication may therefore follow PML treatment in apparently immunocompetent persons.

Clinical improvement within 2 weeks of the onset of cidofovir therapy suggests that cidofovir was effective. However, spontaneous recovery cannot be ruled out. The progression of the MRI white matter lesions detected 3 ½ weeks after onset of cidofovir treatment may have been related to disease progression prior to the initiation of cidofovir therapy. Others have reported clinical improvement in spite of initial worsening of lesions on MRI. MRI performed 4 months after onset of treatment showed marked improvement.

The rapid deterioration prior to treatment with cidofovir is suggestive of IRIS. IRIS is usually explained by reconstitution of a compromised immune system, followed by a strong immune response and inflammation. This may lead to a paradoxical clinical worsening of an appropriately treated infection. IRIS may be seen in HIV positive PML patients who receive antiretroviral therapy, or in PML patients with immunomodulatory therapy and plasmapheresis for removing the immunosupressing agent. Our patient received plasmapheresis, and one might speculate whether removing the natural humoral immune response to the JCV could influence the risk of IRIS.

There are reports that cidofovir may prolong survival among immunocompromised patients with PML while others have failed to disclose
effect of treatment with cidofovir.\textsuperscript{10, 19} One might speculate that cidofovir is more effective the more immunocompetent the patient is.

In conclusion, PML should be considered in immunocompetent patients with typical clinical course and MRI findings. Treatment with cidofovir should be considered as early in the disease course as possible.
References


Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors have no competing interests.

Authors’ contributions

Halvor Naess investigated, treated the patient and drafted the manuscript.

Sovleig Glad investigated the patient and contributed to important revisions of the draft.

Anette Storstein treated the patient and contributed to important revisions of the draft.

Christine H Rinaldo sequenced the JVC genome, performed EIA and contributed to important revisions of the draft.

Sverre J Mørk performed the histology examinations, selected histology images and contributed to important revisions of the draft.

Kjell-Morten Myhr contributed to conception, design and important revisions of the draft.
Figure legends

Figure 1 A. MRI (flair T2) performed on admission showing white matter lesion in the parieto-occipital region on the left side

Figure 1 B. MRI (flair T2) showing progression of white matter lesion 10 days after admission

Figure 1 C. MRI (flair T2) showing progression of white matter lesions in both hemispheres 3 ½ weeks after onset of treatment with cidofovir

Figure 1 D. MRI (flair T2) showing regression of white matter lesions in both hemispheres 6 months after onset of treatment with cidofovir

Figure 2 The biopsy specimen contained cortical grey and subcortical white matter with loose tissue texture (edema), fine caliber vacuolization, swollen, reactive astrocytes (pink cytoplasm in Panel A, hematoxylin and eosin), microglia and lipid macrophages (transformed microglia). Large pleomorphic nuclei of some astrocytes are clearly evidenced. Immunohistochemical staining for myelin basic protein (Panel B, immunoperoxidase (brown)) shows loss of myelin in the white matter lesion. Pleomorphic cells are immunopositive for astrocyte marker glial fibrillary acidic protein (Panel C, immunoperoxidase for GFAP). In-situ-hybridization of the demyelinated lesion (Panel D, original magnification x400) shows enlarged irregular nuclei positive for JC virus.
Figure 3. Schematic illustration of the archetype JCV regulatory regions/NCCR found in urine of healthy people and the rearranged regulatory region demonstrated in the CSF of the PML patient by PCR

Figure 4. JCV and BKV virus-like particle (VLP)-specific IgG levels from the time of patient administration and the following 16 months. The data were obtained retrospectively by EIA. OD 492nm, optical density at 492nm.

Figure 5. Time axis of the development of the disease
Figure 1
Figure 3
Reading problems

Bilateral lower right sided quadrant anopsia
White matter lesions on left side

ADMISSION
Complete anopsia followed by aphasia and paresis of right arm
Brain biopsy: demyelination and atypical astrocytes
Improvement arm paresis

Methylprednisolone, acyclovir, ceftriaxone, plasmapheresis

Cidofovir

Further progression white matter lesions
JCV IgG titer 4x increased. JCV IgM stable

MRI
White lesions on left side
Progression white matter lesions

JCV PCR
Positive JCV PCR brain biopsy and CSF

Serology
Low JCV IgG and IgM titers

Immunology/Histology
Improvement arm paresis
Recovered paresis and aphasia. Improvement of vision.

Epilepsy
Partial bilateral hemianopsia,

JCV IgG titer > 16x increased, JCV IgM stable

Further regression of lesions
Unaltered

Marked regression of lesions

JCV IgG titer > 16x increased, JCV IgM stable

Negative JCV PCR CSF

Figure 5