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Review article

Progressive multifocal leukoencephalopathy, a review and an extended report of five patients with different immune compromised states

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Abstract

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the brain caused by the JC-virus. Both a decreased cellular or humoral immune response can increase the susceptibility for JC-virus induced PML. Not only HIV infected people are at risk, a wide range of otherwise immune compromised patients are a potential target for this virus. This report of five PML patients shows the importance of a clinician's familiarity with this disease and it's presenting symptoms. The presenting symptoms of PML can sometimes mimic worsening of the underlying disease. Although different therapeutic strategies have been tried, the outcomes remain very poor. In this series, treatment with cidofovir appears not to be effective in treating PML, neither in HIV positive nor HIV negative patients. Experimental therapy with leflunomide, after tapering of the immunosuppressive medication, did change the natural course of PML in one patient.

Keywords: Progressive multifocal leukoencephalopathy; Immunocompromised Host; JC polyomavirus; HWA-486 leflunomide; GS-504 cidifovir

1. Introduction

PML is a severe opportunistic infection of the brain, for the first time described in 1958 [1]. This characteristic disease is caused by the JC-virus. This neurotropic virus was identified in 1971 and named after the initials of the patient in which the virus was first isolated [2,3]. This JC-virus should therefore not be confused with the Jamestown Canyon virus, which causes a neurological syndrome characterised by encephalitis and meningitis or the prion induced Jacob–Creutzfeld disease.

The JC-virus is a human polyomavirus. These viruses are members of the papovaviridae family, which are small, nonenveloped viruses with a closed, circular double DNA-stranded genome [4]. The related BK-virus was isolated from the urine of a renal transplant patient who developed urethral stenosis postoperatively. BK-virus and JC-virus share 75% homology at the level of nucleotide sequence and each is 70% homologous to SV40. The two are not cross-reactive serologically and serologic tests for antibodies are able to distinguish between BK- and JC-virus.

The primary JC infection takes place during childhood, apparently without clinical symptoms. Even years after the primary infection, the viral DNA can be found in the urine of healthy individuals [5,6]. In the immune compromised state however, an internal reactivation of the JC-virus infection causes PML.

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Because of lack of direct treatment for the JC infection itself, PML has become one of the most deadly opportunistic infections in patients with AIDS — and otherwise immune-suppressed patients. Although the incidence of PML in the AIDS population decreases [7], probably due to the introduction of highly active anti-retroviral therapy (HAART), the increasing use of new, high dose and strong immune suppressive medication in transplantation medicine and in the treatment of auto-immune diseases is likely to give an increase in the incidence of PML in these groups of patients.

It is therefore essential to be aware of these different risk groups and to recognize the diverse clinical presentations of PML. To demonstrate the relevance of recognizing this deadly infection we present in this report five patients diagnosed with PML. A positive PCR of the cerebral spinal fluid (CSF) for JC-viral DNA supported the diagnosis in all cases. The five patients shown in this report suffered from PML due to five different predisposing factors, representing a wide range of causes of dysfunction of the immune response. The first three patients are described in more detail. The renal transplantation patient is described because of the remarkable presentation and the therapy with leflunomide and both the patient with longstanding Waldenström and the patient with dermatomyositis because of the rare associations of these diseases with PML. Notably, the combination of PML complicating Waldenström or dermatomyositis were both reported only twice previously [8–11].

2. Methods

We identified all CSF samples with a positive PCR for JC-viral DNA from our virological database. PCR on JC-virus was done in our own laboratory from the year 2000 and onward. Only samples negative for other viruses as well as for fungi and bacteria, including tuberculosis, were included. After reviewing the medical history of the corresponding patients, only patients with clinical symptoms and brainscan results compatible with a possible PML, that were primarily analysed and treated in our hospital, were selected. Patients with concomitant other cerebral pathology were excluded.

3. Results

Eight CSF samples with a positive PCR for JC-virus DNA were identified, representing seven patients. All of them were treated in our own hospital and showed signs and symptoms that could be attributed to the diagnosis PML. Two patients were excluded, one because of severe concomitant intra cerebral pathology, namely lymphoma treated with intrathecal chemotherapy complicated by transversal sinus thrombosis and the other because of absence of pathology on the CT and MRI scan of the brain. From the resulting five patients, one patient suffered from dermatomyositis, one from a B-cell NHL, one from Waldenström with mixed cryo-gammaglobinaemia, one was a kidney transplant patient and in one patient PML was the AIDS identifying disease, see Table 1.

4. The patients

Patient 1 is a 77-year-old man who was diagnosed with a severe dermatomyositis in the year 2000. He successfully received intensive treatment with cyclofosfamide, high dose steroids and gamma-globulins till 2004. In that year he was admitted to our hospital because of progressive disability and weakness. No clear neurological abnormalities were identified then. Because of apparent progression of his myositis he was treated with a course of high dose steroids and cyclofosfamide was replaced by sirolimus. Unfortunately soon after discharge the patient became progressively confused and developed a dysarthria combined with severe balance disturbances. The patient's clinical state deteriorated so quickly that admission was necessary. On physical examination we saw a weak and confused man with a dysarthric speech. There was severe trunk ataxia. There was no fever and no lymph nodes were palpable. Blood pressure was 135/70 mmHg and pulse 74 bpm. The skin showed signs of active dermatitis and there were Gottron papules on the hands. Especially the proximal muscles of the trunk were very painful. Reflexes were slightly asymmetric; there was no Babinski's sign. A CT-scan of the brain was performed, showing diffuse white matter changes, without a clear cause. There was no bleeding, infarction, hydrocephalus, meningeal colouring or tumour visible. Cerebrospinal fluid (CSF) showed normal values of glucose, protein and leucocytes. Cultures including those for tuberculosis remained negative and no viral DNA was detected using standard PCR techniques. A second portion of CSF was drawn especially for JC-virus PCR, which clearly showed the presence of JC-virus DNA in the CSF. MRI pictures of the brain showed specific signs indicative of PML [12] (Fig. 1).

Because PML appeared to be the most likely diagnosis, the immune suppressive therapy was stopped. As there were some data suggesting that cidofovir could improve the course in some patients affected with PML [13,14], he was treated with cidofovir 5 mg/kg, with a 1-week interval between doses, each preceded by probenecid and intra venous saline. This therapy was initially well tolerated, but later complicated by progressive renal failure, so a total of only four doses could be given. Despite the treatment the patient experienced rapid and progressive neurological deterioration, with complete ataxia, aphasia, and dysphagia. Within weeks he became obtunded, comatose and he died soon after. Permission for autopsie was not granted.

Patient 2 is a 63-year-old woman who was diagnosed with a cryo-gammaglobulinaemia in November 1997. The patient was referred to our hospital because of her severe hemorrhagic diathesis and an enlarged spleen. In January 1998, morbus Waldenström type IgM-lambda was diagnosed.

Because of the severe bleeding complications our patient received 4 courses cyclophosphamide,vincrisine and prednisone (CVP), followed by fludarabine courses, all with poor results. In 2000 plasmapheresis was tried, followed by two vincristine, doxorubicine and dexamethasone (VAD) courses and one CAD course before peripheral haematopoietic stem cell transplantation. Unfortunately stem cell pheresis failed twice.