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CASE REPORT

# Progressive multifocal leukoencephalopathy in liver transplant recipients: a case report and review of the literature

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## Summary

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the reactivation of the JC polyomavirus in immunocompromised patients. We report a case of PML in a liver transplant recipient and review the other published cases. The clinical course of PML is characterised by a rapid progressive neurological decline coinciding with the presence of white matter lesions on magnetic resonance images. There is no direct antiviral therapy available against the JC polyomavirus. Restoration of the immune response achieved by tapering or terminating the immunosuppressive regimen is the mainstay of treatment at present in transplanted patients. The prognosis remains, however, extremely poor regardless of treatment.

## Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare and severe demyelinating disease of the central nervous system (CNS) caused by a reactivation of the polyoma JC virus [1]. PML typically occurs in immunosuppressed individuals, although the condition can also occur in patients with a mild immunocompromised status, e.g., patients with chronic renal failure or liver cirrhosis. PML was first described in patients with haematological malignancies. The incidence rate increased dramatically during the AIDS pandemic in the eighties. More recently, PML cases have been linked to the drug natalizumab in the treatment of multiple sclerosis (MS) and Crohn's disease, and to the drugs rituximab in the treatment of rheumatoid arthritis and efalizumab in the treatment of psoriasis [1]. There have been sporadic case reports of PML related to solid organ malignancies, granulomatous and inflammatory diseases and solid organ transplantations. We report a case of PML in a liver transplant recipient and review all of the published PML cases in liver transplant recipients.

## Case report

A 71-year-old woman received an orthotopic deceased-donor liver transplant in 2006 for hepatitis-C-virus-related decompensated liver cirrhosis with a Barcelona Clinic

Liver Cancer (BCLC) stage-A hepatocellular carcinoma. The steroid-free immunosuppressive regimen consisted of basiliximab induction therapy in combination with tacrolimus and mycophenolate mofetil maintenance therapy. The initial follow-up was unremarkable. Per protocol biopsies showed an absence of recurrent hepatitis-C-related advanced fibrosis (2007 Metavir F0, 2008 Metavir F1). In June 2009, the patient suddenly developed vertigo and gait instability. She fell from the stairs at home 1 week later and was admitted to the ward for observation. There were no signs of motor deficits on the day of admission. A paresis of the left arm developed on the following day.

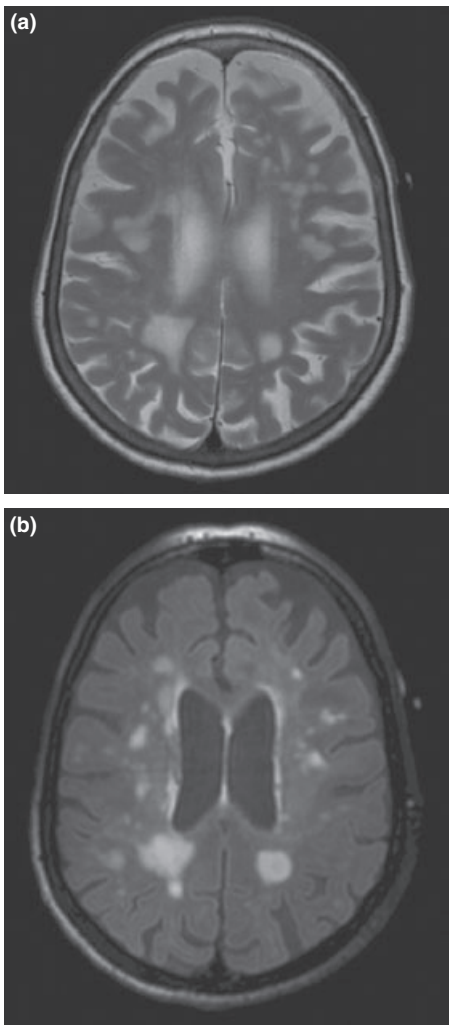


**Figure 1** Brain magnetic resonance imaging. A 4-mm-thick axial Turbo Spin-Echo T2 image (a) and a three-dimensional 0.8-mm-thick fluid attenuated inversion recovery (FLAIR) image (b) through the fronto-parietal region. Multifocal bilateral hyperintense white matter lesions, with an asymmetric distribution pattern, are seen in the periventricular and subcortical regions. The cortex and basal ganglia are spared. The lesions produce no mass effect and are not enhanced on T1-weighted images after intravenous gadolinium administration (not shown).

Brain magnetic resonance imaging (MRI) [T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences] showed multifocal hyperintense white matter lesions with an asymmetrical distribution in the periventricular and subcortical regions without enhancement after intravenous administration of gadolinium (Fig. 1). A semi-recent cerebrovascular accident was initially presumed, and the patient was transferred to the stroke unit for further observation. Over the following days, the neurological deficit progressed into a complete left hemiparesis. Considering the progressive neurological decline and the presence of multifocal white matter lesions on MRI in the immunosuppressed patient, PML was considered in the differential diagnosis. A polymerase chain reaction (PCR) for polyoma JC virus on cerebrospinal fluid was positive (3565 copies/ml). The immunosuppressive regimen was then tapered; the mycophenolate mofetil administration was stopped, and the dose of tacrolimus was tapered from a 1.5-mg total daily dose down to a 0.5-mg daily dose (Fig. 2) with a subsequent decline of the tacrolimus through levels. The neurological decline progressed to a spastic left hemiparesis and prolonged episodes of decreased consciousness over the following weeks. A repeat brain MRI showed progression of the bilateral white matter lesions. Polyomavirus was still detected in a second cerebrospinal fluid tap under the 0.5-mg daily tacrolimus monotherapy. Despite complete cessation of the immunosuppressive therapy, the patient ultimately died 4 months after the appearance of the first neurological symptoms.

## Discussion

The majority of the Western adult population has positive antibodies against polyomavirus because of asymptomatic infection during childhood [1]. The virus remains latent in the kidneys [2]. For many years, it was presumed that these latent virus particles present in the kidney could cause a systemic reactivation. However, recent data have shown that the virus can also be found in the lymphoid organs and can persist in circulating B lymphocytes, pre-B lymphocytes and CD34+ progenitor cells. During periods of profound cellular immunosuppression, the virus can reactivate and spread to the brain [3]. CD34+ haematopoietic progenitor cells carrying the virus are presumed to facilitate the crossing of the blood–brain barrier. A direct route across the blood–brain barrier by infection of brain microvascular endothelial cells has also been postulated [4]. The virus has a tropism for oligodendrocytes, resulting in cell lysis and myelin sheath breakdown that causes progressive multifocal leukoencephalopathy. The clinical course usually consists of diverse progressive sub-acute neurological deficits, including seizures. The outcome is extremely poor, especially in

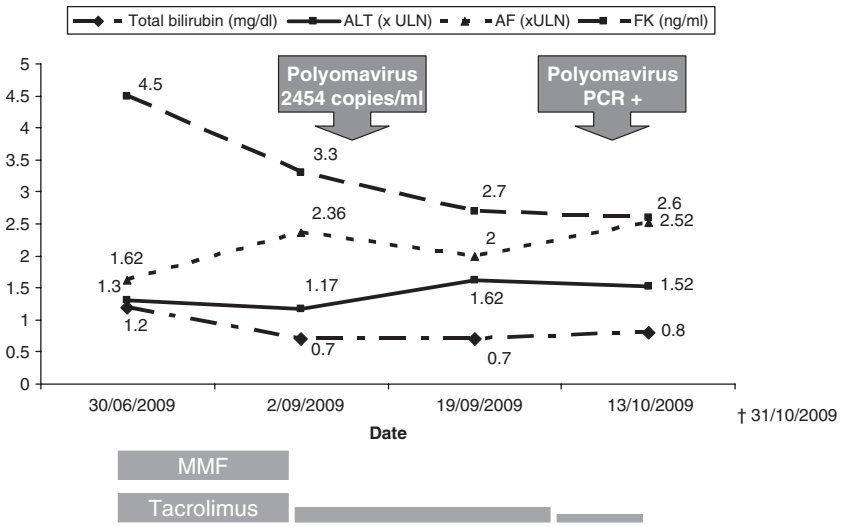


**Figure 2** Polyomavirus replication in the cerebrospinal fluid in relation to the tapering of the immunosuppressive regimen. Despite the tapering and ultimately complete termination of the immunosuppressive regimen, the patient died 4 months after diagnosis.

non-HIV-related PML and in untreated HIV patients, with a 1-year survival rate of 10% [1].

Reports of PML in solid organ transplant recipients are limited. The disease was first reported in renal transplant recipients, and fourteen renal cases in total have been published worldwide. In a Medicare file series of 37 757 kidney transplant recipients, nine cases were observed with a cumulative incidence of 0.027% or 8.8 cases/100 000 person-years of risk [5]. Reports in liver transplant recipients are even more limited. A PubMed and Cochrane library search revealed seven cases [6–12]; we report the eighth patient worldwide. Two transplant centres published an overview of their liver transplant recipients and reported one case in 132 [13] and one in 463 [14] liver transplant recipients, respectively. In lung transplant recipients, three patients have been observed with PML [15], and six have been reported in cardiac transplant patients [16,17].

Table 1 summarises the characteristics of the eight published liver transplant recipients with PML. None of the patients appeared to have received anti-thymocyte globulin. Steroids versus basiliximab induction as part of the initial immunosuppressive regimen does not seem to differ in regards of predisposing patients to JC virus reactivation in this historical series with a limited number of patients. There is no published data available at present that links basiliximab treatment to the development of PML. A majority of the PML patients (five of eight) received a liver transplantation because of a HCV related liver cirrhosis. A direct pathophysiological link between hepatitis C and JC virus has not been demonstrated until now. We therefore presume that this phenomenon could be a reflection of the mere fact that HCV infection was the leading indication for liver transplantation worldwide in the time frame of the reported cases.

Although transmission of polyoma virus from donor to recipient cannot totally be excluded in liver transplantation, we are inclined to think that this is rather unlikely in view of the discrepancy between the high seroprevalence in the general population, of which liver donors are part, and the low incidence of this disease in liver transplant recipients.

The differential diagnosis of new onset neurological symptoms in a transplant recipient should take into account the time window between transplantation and the occurrence of symptoms. Calcineurin inhibitor related leukoencophalopathy, aseptic meningitis caused by OKT3, posterior leukoencephalopathy syndrome, cerebrovascular complications and a multifactorial reversible encephalopathy caused by metabolic disturbances, organ failure and drug toxicity are the most likely causes in the early post-transplant period. In the late transplant period suspicion should be raised for CNS infections, including *Listeria monocytogenes*, *Aspergillus fumigatus* and *Cryptococcus neoformans*, and neoplasms. Chronically immunosuppressed patients are especially at risk of developing CNS lymphoma [18]. From the reported case it seems that PML can present in liver transplant recipients as well in the early as in the late post-transplant period.

The gold standard for the diagnosis of PML is a brain biopsy, although the combination of a recent onset of neurological disease with white matter lesions on MRI and a positive PCR for the JC virus in the cerebrospinal fluid can confirm the diagnosis in the absence of a brain biopsy.

Prognostic markers to identify patients who are at risk for developing PML are lacking: the presence of active JC virus replication in urine or plasma does not correlate with an increased risk to develop PML in liver transplant and natalizumab treated patients [19,20].

**Table 1.** Overview of progressive multifocal leukoencephalopathy cases in liver transplant recipients.

| Sex/age (Ref., year of publication) | Cause of cirrhosis | Immunosuppressive regimen | Development of neurological symptoms | Diagnosis | Treatment | Outcome |
|---|---|---|---|---|---|---|
| F/53 ([6], 1994) | HCV | CsA, AZA, prednisolone *Switched to* tacrolimus, AZA | No neurological dysfunction | Postmortem brain biopsy | No | Died 18 months after transplantation |
| F/55 ([7], 1995) | Cryptogenic | CsA, prednisolone | Combination of cyclosporine-related leukoencephalopathy and PML No neurological symptoms attributed to PML | Postmortem brain biopsy | No | Died 8 months after transplantation |
| M/51 ([8], 1995) | Cryptogenic | CsA, AZA, prednisolone | 8 weeks after Tx | Brain biopsy 15 weeks after TX | Ended immunosuppression regimen Cytarabine | Died 2 weeks after diagnosis and 17 weeks after transplantation |
| F/60 ([9], 2001) | Secondary biliary cirrhosis | CsA, AZA *Switched to* Prednisolone, tacrolimus *Add-on* MMF | 11 months after Tx | JC Virus PCR on CSF 16 months after Tx | Tapered and ended immunosuppression regiment Cytarabine | Died 5 years after diagnosis |
| F/39 ([10], 2005) | HCV | Basiliximab, CsA, MMF, prednisolone *Switched to* tacrolimus, Prednisolone | 8 months after Tx | JC Virus PCR on CSF 8 months after Tx | Tapered immunosuppression regimen Cytarabine | Died 6 weeks after diagnosis and 9 months after transplantation |
| F/59 ([11], 2005) | HCV | Prednisolone, tacrolimus PegIFN and ribavirin 5 months after Tx (9 months) | 18 months after Tx | JC Virus PCR on CSF 18 months after Tx | Tapered immunosuppression regimen Peginterferon Cidofovir | Died 5 months after diagnosis and 23 months after transplantation |
| F/66 ([12], 2009) | HCV | MMF | 113 months after Tx | JC Virus PCR on CSF 120 months after Tx | Tapered immunosuppression regimen | Died (time frame not specified) |
| F/72 | HCV | Basiliximab, tacrolimus, MMF | 34 months | JC Virus PCR on CSF 35 months after Tx | Tapered and ended immunosuppression regimen | Died 4 months after diagnosis and 38 months after transplantation |

CsA, cyclosporine A; AZA, azathioprine; MMF, mycophenolate mofetil; Tx, transplantation; PML, progressive multifocal leukoencephalopathy.

Effective direct antiviral therapy for PML patients is not available at present. Cytarabine adenoside, cidofovir, mirtazapine and mefloquine have *in vitro* antiviral effects against the JC virus. Cytarabine adenoside showed some effect in an open-label study in non-HIV PML patients but no efficacy in a randomised multi-centre open-label study in HIV PML patients. Cidofovir and mirtazapine did not show a survival benefit in (small) clinical trials. Clinical trials with mefloquine are ongoing [1].

Immune reconstitution is the only effective therapy for PML at the moment. The reported liver transplant recipients with an antemortem diagnosis of PML were all treated by tapering or terminating the immunosuppressive regimen. Two of the three patients who were given

cytarabine adenoside died after 3 and 9 weeks, respectively. The third patient who survived for 5 years had a persistent severe neurological impaired status (S. Ryder, Nottingham University Hospitals, personal communication).

## Conclusion

A rapid progressive neurological decline with diffuse white matter lesions on MRI in a liver transplant patient should raise the suspicion of PML. Once the diagnosis of PML is established, the only available treatment consists of tapering and/or terminating the immunosuppressive regimen. The overall survival rate remains extremely poor. Prognostic markers to identify transplant patients who are at risk for developing PML are not available.

## Authorship

XV, WL, JP and FN: manuscript writing. GV, LV and HO: patient care, manuscript writing. JC: MRI image interpretation.

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