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CASE REPORT

Progressive multifocal leukoencephalopathy 11 years after liver transplantation: a case report

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Abstract Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system caused by JC virus. Only ten cases of PML have been reported so far in liver transplant recipients. We present a case of liver posttransplantation PML with characteristic clinical and brain MRI findings, but with an atypical late onset, developed 11 years after transplantation and after single-drug, long-term (8 years), and low-dose (750 mg twice a day) immunosuppression with mycophenolate mofetil (MMF). This is the latest onset of PML associated to liver transplant reported. The present case should help physicians to be aware of PML after transplantation, even in the long term and even under low doses of immunosuppressants, especially MMF.

Keywords Progressive multifocal leukoecephalopathy · Liver transplantation · Mycophenolate mofetil

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare but often lethal demyelinating brain disease caused by the reactivation of JC virus (JCV), an opportunistic DNA virus belonging to *Polyomaviridae*. PML typically occurs in severely immunocompromised patients, such as those with advanced HIV infection, hematologic malignancies, and those receiving immunosuppressive drugs for autoimmune diseases or for prevention of graft rejection after solid organ transplantation (Tan and Koralnik, 2010). Since the first description of PML in a kidney transplant recipient in 1971 (Manz et al. 1971), isolated PML cases have been reported, in order of frequency, after kidney, liver, heart, and lung transplantations (Mateen et al. 2011). Up to now, ten cases of liver transplantation-associated PML have been reported in literature (Verhelst et al. 2011; Ozdemir et al. 2015; Yoshida et al. 2015). Although the incidence of liver transplantation associated PML is very low, its high mortality and the need to establish differential diagnosis with other potential neurological complications (Verhelst et al. 2011) prompt to highlight the relevance of reporting atypical features in any new transplant-associated PML case.

We present an atypical case of a liver-transplanted patient who developed PML 11 years after the transplant and being under minimal doses of immunosuppressive treatment.

Each author states that she/he fulfills the authorship criteria of the International Committee of Medical Journal Editors (ICMJE) recommendations.

Key points •Progressive multifocal leukoencephalopathy (PML) is an uncommon but usually lethal complication of liver transplant recipients linked to immunosuppressive regimens.
•PML should be considered in the differential diagnosis of short- and long-term neurological complications of liver transplantation.

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Case report

A 76-year-old woman received a liver transplant in 2005 due to hepatocellular carcinoma complicating chronic hepatitis C. Thereafter, she maintained triple immunosuppressive therapy with daily 20 mg prednisolone, 3.5 mg tacrolimus, and 2 g mycophenolate mofetil (MMF). Three years after surgery, in the absence of any manifestations of liver dysfunction or graft rejection, immunosuppressive therapy was tapered and simplified to 750 mg MMF twice a day. No transplant-derived

complications were registered until 2016, 11 years after surgery.

In July 2016, the patient was admitted to the emergency department for new onset paresis of the right arm and gait disturbances that developed insidiously few days before admission. On examination, her right arm exhibited a typical spastic posture with paresis, hypertonia, and exaggerated tendon jerks. Right leg's mild weakness was also present. No other neurological signs, headache, or fever were present. There was no history of recent infectious diseases or vaccination.

The first brain magnetic resonance image (MRI) performed during admission (2 weeks after the clinical onset) revealed several bilateral hyperintense lesions on FLAIR and T2-weighted sequences, involving both frontal lobes at cortical-subcortical interphase, thalamus, internal capsule, and cerebellum, with no T1 gadolinium enhancement (Fig. 1). Patient's history of drug-induced immunosuppression, focal neurological manifestations, and MRI findings raised the suspicion of PML, a diagnosis that was supported by a positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR) assay for JCV DNA, with a total viral load of 277 copies/ml [RealStar (®) JCV PCR Kit (Altona Diagnostics, Hamburg, Germany) on Cepheid SmartCycler (®) PCR equipment (Cepheid, Sunnyvale, CA, USA)]. No anti-JCV antibody level testing was performed at that time or during follow-up. Further blood and CSF biochemical and microbiological analyses were all normal or negative, including CSF proteins, glucose and cell count, CSF PCR for human *Herpesviridae*, *Mycobacterium tuberculosis* and *Cryptococcus* spp., blood biochemistry, and HIV serology. PML diagnosis was achieved according to PML diagnostic guidelines (Berger et al. 2013).

Within the first 2 weeks of admission, progressive tapering of MMF was performed, keeping a close clinical and analytical control of liver function. Mirtazapine, attributed to inhibit JCV entry into oligodendrocytes, was added as adjuvant therapy. After complete MMF withdrawal, there was neither liver failure nor clinical improvement. In fact, the patient suffered a progression of the initial mild hemiparesis to a total right hemiplegia, left leg plegia, and dysarthria. A second MRI at that time showed an increase in size of previous brain lesions and new appearing FAIR-T2 lesions, again with no T1 gadolinium enhancement (Fig. 1).

This clinical and MRI progression predicted a poor outcome of PML. Six weeks after admission, the patient was discharged to a palliative care institution, where she died 2 weeks later, 2 months and 7 days after the PML clinical onset.

Discussion

In this case report, we present a patient suffering PML 11 years after liver transplantation and following long-term (8 years) treatment with low doses of MMF. As far as we know, this is the latest onset PML associated to liver transplantation described in literature with the peculiarity of being under long-term low doses of a single immunosuppressive drug (MMF).

PML is an uncommon complication of liver transplantation, with only 10 additional cases reported in literature (Verhelst et al. 2011; Ozdemir et al. 2015; Yoshida et al.

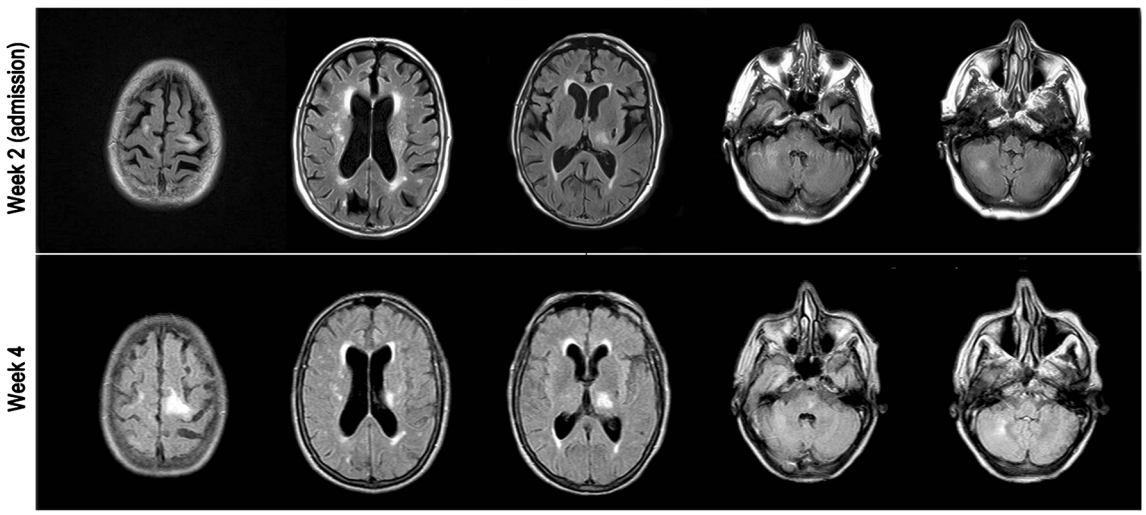

Fig. 1 Brain MRI at diagnosis and at follow-up
Legend: Representative slices from brain MRI, including FLAIR sequences acquired at admission (2 weeks after clinical onset) and 2 weeks later (4 weeks after clinical onset). FLAIR sequence at admission showed several bilateral hyperintense lesions, involving both frontal lobes at cortical-subcortical interphase, left thalamus and posterior limb of internal capsule, and right hemisphere of the cerebellum. Those lesions increased in size 2 weeks later, in parallel with neurological decline, with new appearing FLAIR lesions in left cerebral peduncle, pons, and left corona radiata

2015). However, since PML is not a reportable disease, it is reasonable to consider that similar cases may have occurred but not reported or not recognized. From the reported liver transplantation PML cases, the median time from transplantation to the onset of PML was 11 months (from 2 to 113 months). Most patients were receiving a combination of two or three immunosuppressants, including cyclosporin A, tacrolimus, azathioprine, prednisolone, MMF and/or basiliximab (Verhelst et al. 2011). Only one of those ten cases developed PML receiving MMF in monotherapy (Yehia et al. 2009).

Since most transplant recipients are exposed to different combinations of immunosuppressive therapies, it is unclear whether any one drug increases especially the risk of PML (Mateen et al. 2011). Nevertheless, some authors have proposed a risk classification for immunosuppressive drugs known to be involved in PML, stratifying three risk classes. All the immunosuppressive drugs used for prevention of graft rejection are included in class 3 agents (low risk), except for MMF, our patient's treatment, which is stratified as class 2 agent (Chahin and Berger 2015). In fact, MMF was also the specific drug that was used in monotherapy in the case report that, after our present case, had the longest posttransplantation time delay (10 years) (Yehia et al. 2009).

Although PML in transplant recipients is uncommon, as higher rates of posttransplantation survival are achieved, the total number of cases of PML could increase (Mateen et al. 2011). Hence, reporting the features in any new transplant-associated PML case is needed to disclose the available knowledge. The present case should help physicians to raise suspicion and prompt for earlier diagnosis on PML after transplantation, even in the long term and even under low doses of single-drug immunosuppressant regimens.

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Compliance with ethical standards

Ethical standards statement This case report obtained the ethics approval of Clinical Research Ethics Committee (CREC) of the Hospital Universitario de Cruces, on 25 April 2017.

Assurances All authors declare that the submitted work has not been published before (neither in English nor in any other language) and that the work is not under consideration for publication elsewhere.

Conflict of interest The authors declare that they have no conflict of interest.

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