OMCR

Oxford Medical Case Reports, 2017;2, 15–17

doi: 10.1093/omcr/omx003
Case Report

CASE REPORT

Progressive multifocal leukoencephalopathy after heart transplantation: 4 years of clinically stable infection on low-dose immunosuppressive therapy

Per Sundbom[1,*], Laila Hubbert[1] and Lena Serrander[2]

[1]Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden, and [2]Department of Infectious Diseases and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

*Correspondence address. Department of Cardiology, University Hospital, SE-581 85 Linköping, Sweden. Tel: +46101030000; Fax: +4613145004; E-mail: Per.sundbom@liu.se

Abstract

Progressive multifocal leukoencephalopathy (PML), caused by reactivation of JC-virus is a relatively rare complication seen in patients with compromised immune system. There are no evidence-based treatment available and prognosis is poor. Withdrawal of immunosuppressant can result in further neurological deterioration and for patients with solid organ transplantations, fatal graft rejection. We report a 52-year-old women that presented with seizures within 1 month after heart transplantation. Initial diagnosis was vascular disease. After clinical deterioration 10 months after transplantation, further examinations led to the diagnosis. Minimizing tacrolimus, to a concentration of 2 ng/ml, and extensive physical therapy has improved the physical capacity of the patient. The patient has now been clinically stable for 4 years and extended survival for 5 years. This case adds to the limited adult cases of PML within the population of heart transplant recipients and the need for increased awareness to minimize diagnosis delay.

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection in the central nervous system (CNS) of humans that regained interest after the onset of the human immunodeficiency virus (HIV) pandemic and after the introduction of monoclonal antibody therapy as treatment for multiple sclerosis [1]. However, PML can occur in any individual with a compromised immune system [2]. PML is caused by reactivation of the JC-polyomavirus. The percentage of seropositivity in the population varies in-between studies and transmission, by upper airway infection, usually occurs in childhood or adolescence [1, 3]. After primary infection, the virus sequesters within the cells of the bone marrow, reno- urinary system and blood [1, 4]. Viral reactivation is a result of complex interactions including host predisposition, immunologic function and viral characteristics [3, 4].

For reasons not fully clear, JC-virus can become neurotropic, cross the blood–brain barrier and infect oligodendrocytes in the CNS white matter leading to demyelination and subsequent widespread neurological lesions and cognitive impairment [3]. The molecular pathway of JC-virus infection is the subject of continued investigation [1, 3, 5]. The case report aims to increase awareness of PML and to highlight the difficulty in recognition of symptoms for early diagnosis.

CASE REPORT

A 52-year-old, Caucasian woman with prior surgical correction for congenital transposition and mechanical heart valves was

Received: September 16, 2016. **Revised:** January 1, 2017. **Accepted:** January 19, 2017

heart transplanted in August 2011. Prophylactic antimicrobial agents (sulfamethoxazol/trimethoprime 800/160 mg, fluconazole 50 mg, valaciclovir 250 mg) were given and immunosuppressive therapy was started with thymoglobulin followed by prednisolone, mycophenolate mofetil (MMF) and tacrolimus. Approximately 4 weeks after transplantation, a 1 minute long generalized seizure occurred. Computer tomography (CT) followed by magnetic resonance imaging (MRI), (T1, T2 and fluid attenuation inversion recovery), showed multiple low-attenuation lesions but no signs of hypo perfusion or arterial occlusion. Findings conformed to ischemia from previous embolic events from mechanical valves and hypo perfusion during surgery. Electroencephalography showed no epileptiform activity and the seizure were assigned to previous lesions and medications. Six days later she developed diplopia, apraxia and intermittent headache. Repeated radiology (CT and MRI) showed minor cerebral edema and small suspicion of non-specific lesions in the white matter, still conforming to ischemia and treatment was started with clopidogrel 75 mg, later subsided due to a ventricular ulcer.

The following months her condition steadily improved but suffered multiple side effects of the immunosuppressive therapy that retrospectively withdraw attention from the subtle neurological deficits. Ten months after transplantation the neurologic symptoms became more widespread with vertigo, fatigue, lightly decreased muscle strength, dystaxia and shortly thereafter she deteriorated with right-sided paralysis. A more thorough assessment was initiated were MRI showed additional signs of ischemia while the previous lesions in the white matter had regressed. No source of embolic stroke could be found. Additional 2 months elapsed with multiple examinations (MRI, electroneuronography, electromyography and spinal tap) and 1 year after transplantation, quantitative polymerase chain reaction of the VP1 gene of JC-virus DNA within cerebrospinal fluid (CSF) analysis was positive (1800 copies/ml), and retrospective serology revealed that the patient had anti JC-virus antibodies prior to heart transplantation. The presence of JC- virus in CSF together with the results from MRI resulted in the diagnosis of PML. Due to the physical status of the patient, poor prognosis of the disease and no consent for experimental treatment, palliative care was initiated. To restore immunologic function for virus depression while keeping the risk of graft rejection at a minimal level the immunosuppression were adjusted. The MMF was discontinued due to the infection and leukopenia as well as severe gastrointestinal side effects. Prednisolone was previous discontinued according to the program, which include prednisolone for 3–6 months after heart transplant, if free from graft rejections. As basic immunosuppression tacrolimus was continued at a serum concentration of 2 ng/ml (normal 6–10 ng/ml). The dose was titrated according to neurological symptoms assessed by the patient, since the vertigo and dystaxia deteriorated with increased tacrolimus serum levels.

After drug adjustments her physical status improved and physiotherapy was started.

During 2 years after onset of symptoms, MRIs have shown both progression and regression of the white matter lesions. (Fig. 1) Since 2013, no additional MRI has been performed since the patient has not given consent for further invasive or radiological assessments without any available treatment. The symptoms have stabilized and no further deterioration has occurred and she is since then no longer regarded as a candidate for palliative care. Despite minimal immunosuppression, no clinical, change in biomarkers or echocardiographic signs of graft rejection have been detected. After receiving several hours of physiotherapy daily, her ability to perform activities of daily life has improved to an acceptable level, were she can take brisk walks, though she is not fit enough to work.

DISCUSSION

We here report a rare case of PML in a heart transplanted patient with seizure as initial symptom early after transplantation. PML has an onset that can be subacute, with neurological deficit symptoms showing within days or weeks after viral reactivation (median of 17–24 months after surgery) [6, 7]. As for our case, delayed diagnosis is common, median time is 74 days (1–1643) with vascular disease being the initial diagnosis in 33% [8]. The incidence rate of PML in post-heart and/ or lung transplanted patients is 1.24 per 1000 post-transplant person years and comparable to other immunosuppressed groups [1, 6]. Overall mortality for PML is ~64% 18 months following

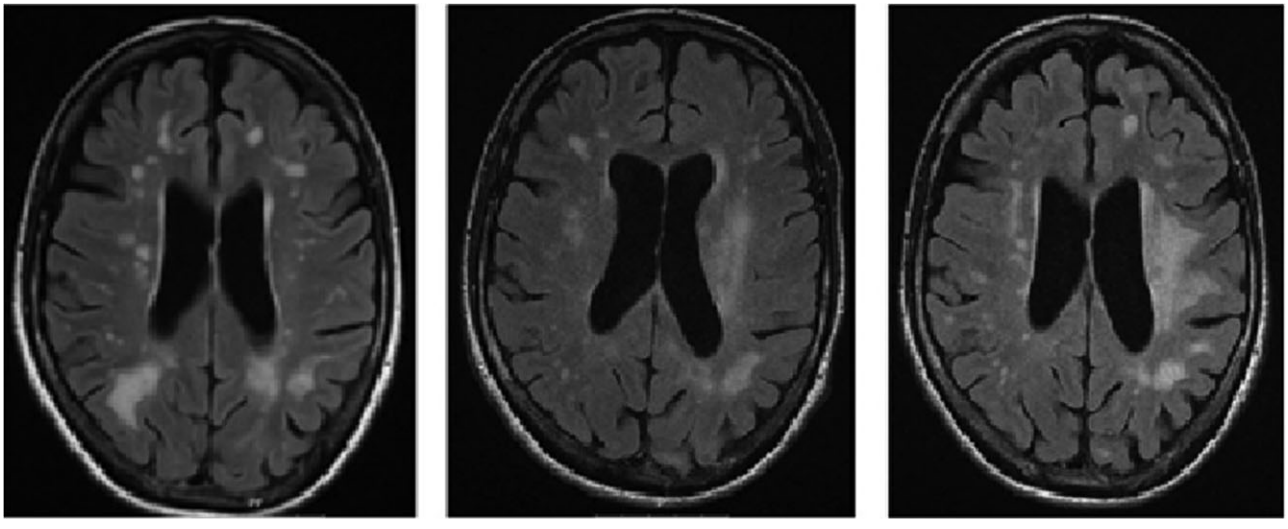

Figure 1: Left: MRI from 2011 shows multiple lesions, most prominent near the posterior cornu on both sides; Middle: MRI from 2012 shows periventricular progression of the lesion on the left side and some regression of the lesion near the right posterior cornu. There are also new widespread lesions in the white matter; Right: MRI from 2013 shows periventricular progression on both sides.

symptom onset, and 29% of those with PML following solid organ transplantation survive a longer period of time, however, suffering from residual neurological damage [6, 7]. The only way to overcome symptomatic infection is by restoring normal function of the immune system. This however, can lead to immune reconstitution inflammatory syndrome (IRIS) that may lead to further neurological deterioration [3, 9]. In our case, survival has now reached 5 years after onset of symptoms and over 4 years since diagnosis. The extended survival might be due to the achievement of equilibrium between opportunistic infection, IRIS and risk of allograft rejection by maintaining low-dose immunosuppressive therapy.

Currently, consensus is lacking for how to manage heart transplanted patients with PML and guidelines are desirable. In heart transplant recipients, regardless of infection, immunosuppression is necessary to prevent fatal allograft rejection and the only cure for PML would be a direct anti JC-virus treatment that is not available [10]. Numerous case reports report some benefit from various treatments but none that is evidence based. This case report shows the difficulty to recognize early onset of PML and therefore treat alternative initial diagnosis. Greater knowledge of PML in physicians treating transplanted patients might lead to minimized diagnostic delay, earlier tailored immunosuppression, physiotherapy and perhaps to favorable outcome.

GUARANTOR

Dr Per Sundbom, Dr Lena Serrander and Dr Laila Hubbert.

CONFLICT OF INTEREST STATEMENT

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript, or any other conflict of interest to disclose.

FUNDING

There were no sources of funding.

ETHICAL APPROVAL

No approval is required.

CONSENT

A fully written consent to publish the case report was obtained from the patient.

CONTRIBUTION DISCLOSURE

P.S., L.H., L.S.; text and review of the literature.

DISCLOSURE

None of the authors has any financial or commercial interest to declare.

REFERENCES

1. Wollebo HS, White MK, Gordon J, Berger JR, Khalili K. Persistence and pathogenesis of the neurotropic polyomavirus JC. *Ann Neurol* 2015;**77**:560–70.
2. Monaco MC, Major EO. Immune system involvement in the pathogenesis of JC virus induced PML: what is learned from studies of patients with underlying diseases and therapies as risk factors. *Front Immunol* 2015;**6**:1–5.
3. Pinto M, Dobson S. BK and JC virus: a review. *J Infect* 2014;**68**: S2–8.
4. Durali D, de Goer de Herve MG, Gasnault J, Taoufik Y. B cells and progressive multifocal leukoencephalopathy: search for the missing link. *Front Immunol* 2015;**6**:241.
5. Maginnis MS, Nelson CD, Atwood WJ. JC polyomavirus attachment, entry, and trafficking: unlocking the keys to a fatal infection. *J Neurovirol* 2015;**21**:601–13.
6. Mateen FJ, Muralidharan R, Carone M, van de Beek D, Harrison DM, Aksamit AJ, *et al.* Progressive multifocal leukoencephalopathy in transplant recipients. *Ann Neurol* 2011;**70**:305–22.
7. Shitrit D, Lev N, Bar-Gil-Shitrit A, Kramer MR. Progressive multifocal leukoencephalopathy in transplant recipients. *Transpl Int* 2005;**17**:658–65.
8. Miskin DP, Ngo LH, Koralnik IJ. Diagnostic delay in progressive multifocal leukoencephalopathy. *Ann Clin Transl Neurol* 2016;**3**:386–91.
9. Lima MA. Progressive multifocal leukoencephalopathy: new concepts. *Arq Neuropsiquiatr* 2013;**71**:699–702.
10. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Ther Adv Neurol Disord* 2015;**8**:255–73.