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Progressive multifocal leukoencephalopathy in a kidney transplant recipient — case report and review of the literature

Abstract

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the JC virus (JCV). Most cases have been reported in severely immunocompromised patients, including transplanted patients. Lesions in the white matter are the cause of neurological dysfunction. Variable neurological and psychiatric symptoms may be observed at the time of presentation. The aim of this paper is to present a case of a 58 year old female recipient of an unrelated living kidney graft, who developed PML 47 months after transplantation and a review of current literature. At the time of transplantation patient received antithymocyte globulin induction (ATG, Fresenius) and was then maintained on a triple immunosuppressive regimen (mycophenolate mofetil, tacrolimus and prednisolone). She presented with an abrupt onset of diplopia, vertigo and paraesthesia of the right side. MRI revealed widespread lesions in the white matter. Marked hyperproteinaemia, hypergammaglobulinemia and lymphocytosis was found in cerebrospinal fluid. Patient's neurological status deteriorated over following two months. Suspicion of PML was raised and the dosages of mycophenolate mofetil and tacrolimus were considerably reduced. Most of the symptoms abated and 12 months later the patient complained only of occasional headaches. Repeated MRI disclosed near complete resolution of white matter lesions. Graft function temporarily worsened but then stabilized. Conclusions: 1. PML should be considered in differential diagnosis of psychiatric and neurological symptoms in transplant recipients. 2. Minimizing of immunosuppressive therapy may lead to regression of this potentially fatal disease.

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Keywords: progressive multifocal leukoencephalopathy; renal transplantation; immunosuppression

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a potentially fatal demyelinating disease of the central nervous system affecting mostly immunocompromised individuals. Initially he majority of reported PML cases were reported in patients with acquired immune deficiency syndrome (AIDS), but later evidence of PML cases in patients with immunological deficiency induced by immunosuppressive therapy has been accumulating. Those include patients with autoimmune diseases (especially those treated with biological therapy) [1–3], but also bone marrow and solid organ transplant recipients (mostly lung, heart, intestine and dual organ transplants) [4, 5].

In addition there are some reports of PML diagnosed in both deceased and living kidney recipients [6–13]. Some evidence point into the role of mycophenolate mofetil based immunosuppression in facilitating replication of JC virus. [14] A recent population based study from France has shed some light onto epidemiology and predisposing factors of PML [15].

PML is considered to be caused by the replication of JC virus (JCV) of the polyomaviridae family. Several Polyoma viruses have been recognized to affect humans: BK,

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Table 1. Donor and recipient data at the time of transplantation

	DONOR	RECIPIENT
AGE	46	48
HLA A, B, C, DR	A-1,2; B-5(51), 8; C-w6, w7; DR-3(17), 7;	A-2, 11; B-27, 40(60); C-w2, w3; DR-2(16), 4;
CMV	IgM-(negative); IgG-(positive)	IgM-(negative); IgG-(positive)
EBV	IgM-(negative); IgG-(positive)	IgM-(negative); IgG-(positive)

JC, SV40 and more recently KI (Karolinska Institute), WU (Washington University) and Merkel cell polyomaviruses. Small, icosahedral, DNA-based, lipoprotein envelope lacking Polyoma viruses often persist as latent infections. Beside JC virus, DNA of WU and KI viruses have been identified in autopsy brain samples of HIV positive individuals with or without histopathology consistent with PML [8]. The JC virus demonstrates tropism to the neuroglia cells, where in a condition of inadequate defense mechanisms, it can multiplicate. This in turn results in destruction of the glia cells leading to formation of lesions in the white matter and neurological dysfunction [17, 18].

Clinical manifestations of PML vary between individuals as do the affected brain areas. Many different neurological and ophthalmological, as well as psychiatric, symptoms may be observed. A tendency for later manifestation of the disease in kidney recipients (with the median time to onset being 30 months) compared to other organ and bone marrow transplant recipients has been observed [19].

In this paper we present a case of a 48 year old female recipient of an unrelated living kidney graft, who possibly developed PML 47 months after transplantation.

CASE REPORT

Patient's underlying cause of end stage kidney disease was the primary hyperparathyroidism. Medical history revealed chronic pancreatitis, hypothyroidism and right nephrectomy due to recurrent urinary tract infections (UTI).

The patient received her renal allograft from an unrelated living donor after 16 months of hemodialysis. Donor and recipient data are presented in Table 1. At the time of transplantation patient received anti-thymocyte globulin induction (ATG, Fresenius, total dose 600 mg) and was then maintained on a triple immunosuppressive regimen (tacrolimus, mycophenolate mofetil and prednisolone). Acute biopsy proven graft rejection (Banff IB) was diagnosed early post transplantation; treated successfully with methylprednisolone pulses (dose total: 4,0 g i.v.). Satisfactory graft function (stable serum creatinine levels of 1.2 mg/dL) was established. New onset diabetes was diagnosed and insulin therapy commenced at the time of discharge. Because of recurrent UTI left nephrectomy was performed, however this did not solve the problem. Normocytic anemia persisted in lab findings. Posttransplant medical history was otherwise unremarkable. Prednisolone dose was gradually reduced to 5 mg OD over 12 months. Dosage of MMF remained unchanged during the whole posttransplant period, 0.5 g BID. Tacrolimus doses were gradually decreased and blood levels kept in the range between 5 and 7 μg/L.

47 months post transplantation the recipient was admitted to neurology department complaining of sudden onset of diplopia and vertigo. Several weeks earlier the patient had surgery due to glaucoma. Neurological examination revealed strabismus, paresthesia of the right side, right cerebellar syndrome and the right eye bulb directed upward with impaired movement; there was no impairment regarding the left eye bulb. MRI scan revealed nonspecific changes of signal in T2 and FLAIR sequences involving thalamus, pons and brain stem white matter, along Sylvian aqueduct to the fourth cerebral ventricle (Fig. 1, 2). Computed tomography (CT) scans were unremarkable. Infiltratory etiology of changes or gliomatosis were presumed. Analysis of cerebrospinal fluid (CSF) revealed marked hyperproteinemia, hypergammaglobulinemia and pleocytosis with 78% of cells identified as lymphocytes. Cytomegalovirus (CMV) pp65 antigenemia was negative. Latex tests for the presence of Candida, Aspergillus fumigatus and Cryptococcus neoformans antigens in blood samples were negative. Results of cytological examination and immunophenotyping of CSF cells were not conclusive for proliferative dis-

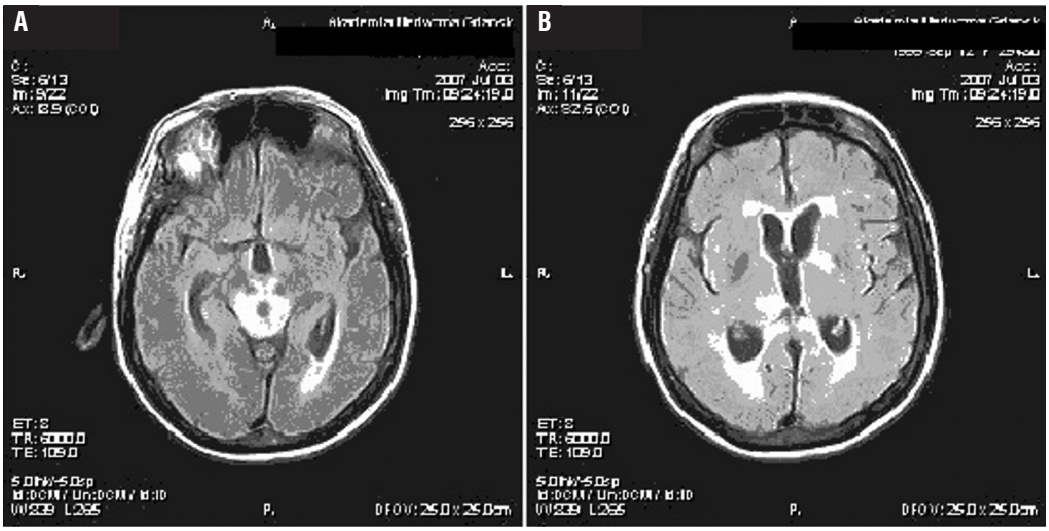

Figure 1a, b. T2 weighed FLAIR sequences of mesencephalon reveal incorrect signal in posterior pons area, basal area of thalamus (more prominent on the right side) and medial area of left thalamus; downward brain stem, along Sylvian aqueduct to the apex of the fourth ventricle

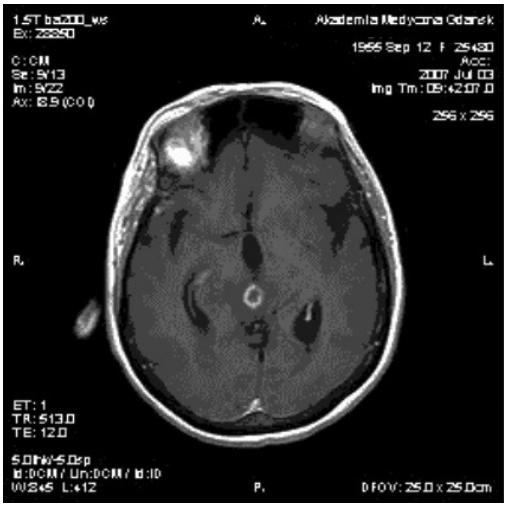

Figure 2. After intravenous administration of contrasting agent small foci of signal enhancement are noticeable at the basis of the third ventricle and in the posterior limb of the left internal capsule; discreet signs of CSF permeating are also present

ease. Biopsy was not performed due to the location of brain pathology (mainly subcortical and mesencephalon white matter).

During her stay at the neurological unit the patient's general condition deteriorated gradually. On admission to the transplant unit, two months after the onset of neurological symptoms, the patient was bedridden, feverish, disorientated, somnolent, nauseous, demonstrating urine and feces incontinence. Physical examination revealed stable vital signs, abdomen tender and flatulent, hydrothorax, some edema of the lower limbs, dry and desquamating skin, cachexia and hypotonia. Nystagmus and decreased muscular strength were found in neurological examination. Consequent observation disclosed apathy, mood swings, memory impairment. The patient complained of headaches and pruritus. Increased levels of WBC, CRP, PCT and creatinine (2.5 mg/dL) were found. Blood and urine cultures were positive (*Acinetobacter baumani*), CMV pp65 antigenemia in blood sample in a repeated assay was positive. Analysis of TSH, fT4 and fT3 confirmed preexisting hypothyroidism. Antibodies to Toxoplasma class M and G were negative. CD4+ and CD8+ lymphocyte counts and their ratio were similar to the results found in AIDS patients (Tab. 2).

At this stage despite lack of definite diagnosis, immunosuppression was reduced; MMF dosage to 250 mg BID, tacrolimus serum levels to 1–2 μg/L.

Parenteral nutrition was commenced due to persistent diarrhea/feces incontinence. The patient received antibiotic and gancyclovir in therapeutic doses for 21 days. Follow-up assessment of pp65 antigen was negative. Tuberculostatic treatment with rifampicin and isoniazid was induced on empirical bases and continued for a period of six months. Thyroxin supplementation was increased and normalization of fT4 was achieved.

Rehabilitation process helped the patient to her feet within a month, the largest difficulty to overcome was weakness of thigh muscles and difficulties in balance control. Gradual improvement of the patient's medical condition was observed, however recurrent UTI and sub-

Table 2. Assessment of lymphocyte subpopulations discloses deep deficiency within CD4 positive lymphocytes at months 2 and 5 post substantial immunosuppression reduction

Lymphocyte subpopulation	52nd month post TR	55th month post TR	Lab reference values
Lymphocytes	1.65 G/L	0.94 G/L	1.3–1.9 G/L
CD4+ Lymphocytes	0.28 G/L [17%]	0.21 G/L [22%]	0.6-0.98 G/L [43-54%]
CD8+ Lymphocytes	0.77 G/L [53%]	0.5 G/L [53%]	0.42–0.66 G/L [28-37%]
CD4+/CD8+	0.3	0.4	1.2–1.9
CD3+ T Lymphocytes	1.16 G/L [70%]	0.71 G/L [75%]	1.0–1.5 G/L [71–79%]
Activated T Lymphocytes	0.25 G/L [15%]	0.26 G/L [28%]	0.052–0.19 G/L [4–10%]
B Lymphocytes	0.21 G/L [13%]	0.04 G/L [4%]	0.16–0.27 G/L [11–17%]
NK Lymphocytes	0.28 G/L [17%]	0.16 G/L [17%]	0.13–0.25 [8–15%]

sequently enterocolitis (*Clostridium difficile*) interrupted the process.

Twelve months after the onset of neurological symptoms the patient complained of occasional headaches and pruritus. MRI scans disclosed complete resolution of white matter lesions. Due to graft dysfunction (serum creatinine 3 mg/dL; eGFR 18 mL/min), graft biopsy was performed; findings were not specific (lymphoid interstitial infiltrates, focal glomerulosclerosis and tubular atrophy). Over the period of fourteen months after the biopsy, graft function improved (serum creatinine 1.6–1.8 mg/dL, eGFR 30–35 mL/min). Immunosuppression was maintained with MMF (CellCept) 250 mg BID and tacrolimus prolonged release 0.5 mg (Advagraf, Astellas) OD.

At 18 months patient presented without complaints. Follow-up MRI scans showed no infiltratory changes in the brain stem and thalamus. Numerous small foci were noticeable, hyper intensive in T2 weighed sequences, located in deep white matter paraventricular in frontal and parietal lobes.

DISCUSSION

PML is a demyelinating disease of the central nervous system considered to be caused by the JCV of the Polyomaviridae family. Besides JC virus', DNA of WU and KI viruses have been identified in autopsy brain samples of HIV positive individuals independent of histopathology diagnosis of PML [8]. Most of the reported cases of PML are of patients with AIDS or hematological neoplasms. Clinical outcome was unfavorable in most cases. Growing number of reported PML cases in patients on immunosuppressive treatment (such as transplant recipients) may result from more potent therapy, but also better diagnostic methods. The average prevalence of anti-JCV antibodies in the polish population is 46%, rising to 63.6% at the age of sixty. Out of four JCV genotypes identified, type 4 is the most common in the Polish population [16]. A study from Switzerland reported 58% prevalence of JCV antibodies class G in healthy blood donors, rising to 68% in those older than 50 [21, 22].

Clinical manifestations of PML vary. The following neurological and psychiatric abnormalities have been described: focal motor neurological deficits starting from "weakness" and including tetra paresis; changes in mental status (apathy, confusion, disorientation, hallucinations, memory impairment); seizures; visual symptoms; ataxia, extrapyramidal symptoms; alexia, dyscalculia, apraxia, dizziness, urine and feces incontinence [19, 23–25]. Several reported PML cases in transplant recipients started with visual dysfunction. The diagnosis was delayed as the symptoms were often attributed to cataract and steroid treatment [19, 24]. Time of onset of PML in transplant recipients varies from early post transplantation period to 132 months. However, most cases develop within the first two years following transplantation. In kidney recipients longer period to disease onset (with the median of 30 months) has been observed [19].

In the case described in this paper visual symptoms were present at onset. The patient's medical condition gradually deteriorated and a number of additional neurological and psychiatric manifestations ensued (urine and feces incontinence, changes in mental status: apathy, emotional swings, confusion, memory

impairment) prior to the suspicion of PML and consecutive reduction of immunosuppressive regimen. Weakness, mainly affecting thigh muscles and difficulties in posture control can also be considered typical clinical appearance of this focal demyelinating disease of the central nervous system. Additional problems hampered diagnostic and therapeutic process (UTI, cytomegalovirus infection, hydrothorax of uncertain etiology and hypothyroidism). Some could be ascribed to excess immunosuppression, though *Acinetobacter baumani* etiology suggests UTI secondary to bladder catheterization.

PML cases have been reported in transplant recipients with immune deficiency secondary to regimens including calcineurin inhibitors, mycophenolates, sirolimus, azathioprine, monoclonal and polyclonal antibodies [14, 19, 23–25]. A USRDS related study identifying 37 757 primary transplant recipients [14] reported nine cases of PML — all receiving MMF. The patient we present received immunosuppression composed of ATG in induction, prednisolone, mycophenolate mofetil and tacrolimus. During the early posttransplant period she received additional pulses of methylprednisolone as the treatment of acute graft rejection. The dosage of MMF was reduced to 1.0 g per day, the dosage of tacrolimus was gradually reduced throughout the posttransplant period. For two years prior to the outset of neurological disturbances, serum tacrolimus concentrations were below 6 μg/L. Both the dosages and the serum concentration of immunosuppressive drugs did not indicate over-immunosuppression until the onset of the devastating symptoms of neurological disease. At that time assessment of lymphocyte subpopulations revealed low CD4 positive lymphocytes count. CD4+/CD8+ ratio was similar to the one found in patients with AIDS. Such status suggests increased possibility of reactivation of Polyomaviridae and explains other opportunistic infections (CMV). Lymphocyte CD4+/ /CD8+ ratio remained extremely low for several months following substantial immunosuppression reduction. Cases like this indicate that methods of assessing the immune system function beyond levels of drugs are necessary in transplant recipients.

Confirmation of suspected PML often proves difficult [26]. Differential workup of neurological deficits typically begins with neuroimaging. CT is not sensitive for diagnosing this neural infection. The appearance of abnormalities in MRI scans opposed to discreet unspecific changes in CT scans is typical [27–30]. MRI imaging contributes substantially to the diagnosing process. T2 weighted and protein density sequences disclose asymmetric hyper intensive areas located mainly subcortically, also in the cerebellum, pons and the brainstem, with no mass effect or evident contrast enhancement. Some reports indicate later appearance of enhanced areas as signs of immune response and infiltrations and indicate that this enhancement is a favorable prognostic factor. In the presented case, CT scanning of brain tissue did not disclose multiple lesions, which were visible in T2 weighed and FLAIR sequences of MRI imaging. T2 weighed FLAIR sequences revealed incorrect signal in: posterior pons area, basal area of thalamus and medial area of left thalamus, in the brain stem and along Sylvan aqueduct to the apex of the fourth ventricle with no contrast enhancement of the above mentioned severe white matter lesions. Gadolinium enhanced MRI showed small foci of signal enhancements at the basis of the third ventricle and in the posterior limb of the left internal capsule. Discreet signs of CSF permeating were noticeable.

Routine analysis of CSF might be found within laboratory reference values, however elevation of protein and albumin levels have been noted. Methods of virus identification, such as polymerase chain reaction (PCR) for JVC DNA and Polyomaviridae specific large T-antigen, are currently a target of investigational studies on JCV [18]. PCR for the JCV DNA in CSF has a reported sensitivity of 72–93%, specificity of 90–100%. JCV DNA has been identified in brain tissue of transplant recipients lacking any neurological dysfunctions and is higher than in CSF. Clinical interpretation of viral genome or protein presence without clinical symptoms, as signs of replication and reinfection, needs further investigation. In case of this patient slight changes in protein levels in CSF were observed. CSF was not tested for viral presence. In clinical practice only a limited number of sites have routine access to JCV identification in CSF or in brain tissue. Brain biopsy was not performed in our case due to localization of the changes in deep subcortical white matter and risk of complications. Brain stem or sub cortical white matter biopsy might prove technically difficult and should always be outweighed with the possible side effects and patients' clinical status. If available, the morphology of brain tissue typi-

cally discloses destruction of oligodendrocytes, forming lesions occurring most often in cerebral hemispheres, cerebellum and brainstem. Deep grey matter structures in general seem to be unaffected. Microscopic evaluation reveals multifocal demyelination with axon sparing and giant bizarre astrocytes with large pleomorphic nuclei and large hyperchromatic oligodendrocytes containing nuclei packed with viral particles at the periphery of the affected areas. Incidental involvement of grey cortical matter was noted [19]. An empirical diagnosis is often necessary as delayed treatment might prove fatal.

In our case, at the time of marked neurological symptoms, no attempts to identify the virus' presence within brain tissue or CSF or blood samples were possible. Nor did we test for JCV antibodies. The suspicion of diagnosis of PML in this kidney-recipient was brought forward from retrospect and based upon clinical manifestation and neuroimaging disclosing central nervous system lesions typical in location and character in MRI. Also the signs of serious immunodeficiency made the diagnosis probable. The satisfactory clinical outcome, as well as the regression of white matter lesions in NMR scans following considerable reduction of immunosuppressive regimen, strengthened the supposition of PML diagnosis in our patient.

If untreated, PML gradually progresses to a fatal outcome in most cases. From the time of onset, the observed progress can be rapid (days) to mild and gradually worsening. However, in cases of rapidly progressing disease, neurological disturbances preceding deterioration were described [19, 22–24]. In several cases visual symptoms preceded and were often attributed to co-existing ophthalmopathy. Total strength of immunosuppression, rather than specific drug regimen were considered as a risk factor. However some data points towards the use of mycophenolate mofetil and biological agents [31–33].

Discontinuation or reduction of immunosuppression offers a possibility of reversing the progress of this disease. Cases with total or partial resolution of white matter lesions previously described in MRI scans and also total or partial regression of neurological dysfunction with time have been reported [24–32].

The role of antiviral medications in treatment of PML is yet to be established. Several cases of successful outcomes of this disease following cidofovir therapy combined with reduction of immunosuppression and mirtazapine in immunocompromised patients have been reported [34–36]. An anectodal report from Japan suggested favorable outcome after combination treatment with antimalarial drug mefloquine and anti-serotonin agent mirtazapine in bone marrow transplant recipient with PML [37]. Some reports showing promising results with the use of specific allogeneic T-cell therapies have been recently published [38, 39]. The risk of immune reconstitution syndrome must be taken into consideration [40].

In the case of our patient, substantial immunosuppression reduction (tacrolimus and MMF) two months after the onset of first visual symptoms, was followed by slow recovery. The patient was simultaneously treated with gancyclovir for co-existing CMV reinfection, with rifampicin and isoniazid for a suspected Mycobacteriacae infection, thyroid gland hormone supplementation was monitored, several courses of antibiotic therapy for UTI and enterocolitis followed. Lymphocyte CD4+/ /CD8+ ratio remained extremely low for a long period despite substantial reduction of immunosuppression. Recovery period lasted several months; clinical resolution of neurological symptoms was observed, also NMR imaging of brain structures revealed near complete resolution of white matter lesions.

Clinical symptoms mentioned above are not specific to PML, yet typical for this neuro-infection. In addition the appearance of white matter lesions found in MRI images of brain structures is not specific, but typical for the disease. The character and gradual radiological and clinical regression of the described abnormalities in view of immunosuppressive protocol reduction, make PML diagnosis highly probable even without attempting viral presence confirmation. MRI scan might prove a helpful tool in monitoring the disease and therapeutic progress and aid clinical observations.

Although the topic of PML in transplant recipients emerges, the number of published cases is limited. This entity requires further investigation in transplant recipients. The factors predisposing to the development of this demyelinating and potentially fatal neuroinfection need to be identified. The question whether its diagnosis in subclinical stages and earlier intervention influences outcomes remains open [43]. Finally consensus regarding approach to treatment must be sought. Although not all reported cases had a favourable outcome, it may

be concluded that reduction or discontinuation of immunosuppressive regimen improves prognosis in these cases.

CONCLUSIONS

In conclusion we would underline that:

1. PML should be considered in differential diagnosis in transplanted patients presenting with neurological or psychiatric disturbances.
2. Discontinuation or minimization of immunosuppressive therapy may lead to regression of this potentially fatal disease.
3. Transplant patients presenting recurrent bacterial and viral infections, may be also prone to the replication of JCV.

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