

Neurotoxicity that May Mimic Progressive Multifocal Leukoencephalopathy in Patient with Transplanted Kidney

Meri Matijaca¹, Jadranka Vlašić-Matas², Stipan Janković³, Irena Pintarić¹ and Anton Marović¹

¹ Clinical Department of Neurology, University Hospital Split, Split, Croatia

² Clinical Department of Internal Medicine, University Hospital Split, Split, Croatia

³ Clinical Department of Diagnostic and Interventional Radiology, University Hospital Split, Split, Croatia

ABSTRACT

We present the 55-year old woman who has had kidney transplantation three times. She has been treated with immunosuppressive therapy and lamivudine for hepatitis B and C. Nine years after the last transplantation she showed neurological symptoms that presented in the form of confusion and epileptic seizures of the grand mal type. A brain MRI showed large oval zones of hyperintense MR signal in T2-weighted image and hypointense in T1-weighted image around the frontal horns of the lateral ventricles, bilaterally and in both cerebellar hemispheres. After reduction in immunosuppression and the exclusion of lamivudine from therapy, the patient was stable with normal neurological status during the course of next five years. We start from the assumption that the concomitant use of cyclosporin with mycophenolate mofetil and lamivudine, despite normal concentrations of cyclosporin, might cause the accumulation of toxic metabolites and lead to neurotoxicity that mimics PML in a chronic viral environment.

Key words: immunocompromised patient, immunosuppressive therapy, kidney transplantation, neurotoxicity, progressive multifocal leukoencephalopathy (PML)

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rapidly progressive degenerative demyelinating disease that occurs in immunocompromised patients. The disease was initially identified as a rare complication of chronic lymphocytic leukemia and Hodgkin's disease. Later PML was reported in association with other leukemias and lymphomas, cancer chemotherapy, immunosuppression as well as with chronic inflammatory diseases including AIDS. PML is a progressive condition, although prolonged survival and clinical remission have been described in both AIDS-related and non-AIDS-related diseases.

The disease was initially identified by Astrom and colleagues as a rare complication of chronic lymphocytic leukemia and Hodgkin's disease¹. Subsequent cases were reported in association with other leukemias and lymphomas, with cancer chemotherapy, with immunosuppression for rheumatic disease or after organ transplantation, and with chronic inflammatory diseases such as

sarcoid, tuberculosis, or nontropical sprue². It is now estimated that 4% of all patients with AIDS will develop PML³.

Suspicion of progressive multifocal leukoencephalopathy is aroused by characteristic clinical and neuro-radiologic abnormalities in an immunocompromised patient. Aphasia, dementia, and confusional states are typical manifestations.

In PML, neuroimaging studies demonstrate abnormalities of the cerebral or cerebellar white matter (hypodense white matter by computerized tomography and high-signal intensity of white matter by T2-weighted MRI). These abnormalities represent demyelinating lesions in the deep white matter⁴.

In our case we present a specific therapeutic approach in which a reduction in immunosuppression, despite of the risk of kidney rejection, may bring to a recovery of cerebral functions.

Case Report

A 55-year old female patient hospitalized in the Department of Neurology (November, 2001) with clinical signs of grand mal seizures. Heteroanamnestic data showed she had memory impairment and disordered behavior, developed in a period of three months. She was nervous, confused and forgetful. She had difficulty with dressing herself and suffered of disorientation in time, as well as insomnia. She experienced some neuralgic symptoms of low limb weakness and dizziness. She was afebrile all the time.

According to the patient's medical history she suffered from chronic glomerulonephritis. She developed chronic renal failure at the age of 33 and was treated with chronic hemodialysis. In this period she became B virus hepatitis positive.

Renal transplantation was performed in 1980 from a living donor (her sister). Seven months later, graft failure developed due to renal artery stenosis. Later, in 1988, she underwent a cadaveric renal transplantation. Unfortunately, renal vein thrombosis developed, and the kidney transplant was removed on the ninth postoperative day. In 1992 cadaveric renal transplantation was performed again. After that transplantation she became C virus positive.

The immunosuppressive regimen during the course of six years after transplantation included azathioprine, cyclosporin and prednisone. After that period azathioprine was replaced with mofetil mycophenolate due to the worsening of hepatal function. Consequently, lamivudine was additionally included in the therapy.

From then on she began taking mofetil mycophenolate (Cell-Sept) 500 mg twice daily, cyclosporin (Sandimmun Neoral) 75 mg twice daily (2.5 mg/kg/day), prednisone (Decortin) 10 mg, lamivudine 100 mg daily, nifedipine 5 mg twice daily, atenolol 25 mg.

The therapy did not change for the next three years, except for a reduction in the lamivudine dose to 150 mg intermittently during the last six months before admission to the neurology department.

In the nine years after transplantation she had a reactivation of CMV twice, and Herpes zoster a year prior to hospitalization.

On admission in the Department of Neurology, in November 2001, the patient exhibited clinical signs of grand-mal seizures. Diazepam was given intravenously. A general physical examination was normal and no nuchal rigidity was present. Her pupils were normally reactive with forced deviation of the eyes to the left. No disorders of facial nerves were discovered. Motor examination showed no weakness in the upper and lower extremities, but muscle tone was decreased and tendon reflexes were attenuated. Plantar responses were normal. Clouding of consciousness was diagnosed.

The neurological therapy that followed included carbamazepine 200 mg twice daily. Her condition improved, and she was free of seizures.

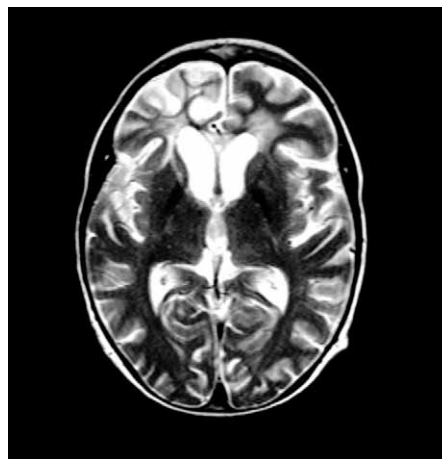


Fig. 1. Brain MRI at admission: Large oval zones of hyperintense MR signal in T2- weighted image.

Urgent evaluation by CT of the head found hypodense white matter lesions with no intravenous contrast enhancement, located at both frontal regions as well as in the white matter of the cerebellum. These changes were assigned as multifocal leukoencephalopathy.

A brain MRI at admission showed large oval zones of hyperintense MR signal in T2- weighted image and hypointense in T1- weighted image in both cerebellar hemispheres, around the frontal horns of the lateral ventricles, bilaterally. In the left hemisphere, frontally, cortical changes were found, i.e. hyperintense MR signal in T2-weighted image and hypointense in T1-weighted image. There were no gadolinium contrast imbibitions in these particular zones (Figure 1).

An EEG was arrhythmic with signs of paroxysmal changes in the frontal regions, more emphasized at the right side. Her fundus examination was normal.

On the Folstein Mini Mental Status she scored 30/32.

The laboratory data, obtained at admission are presented in Tables 1 and 2. Cyclosporin concentration was 67.3 ng/mL (cyclosporin whole blood, FPIA-Abbot) and serum level of carbamazepine 11.7 ng/mL.

Genome detection of polyomavirus JC from cerebrospinal liquor (PCR) as well as detection of HHV6 and CMV (PCR) were found negative. Serology for toxoplasmosis and human immunodeficiency virus (HIV1/2) were negative, while hepatitis B and C remained positive.

Based on the above evidence we decided to reduce the immunosuppression for the patient. Mofetil mycophenolate was discontinued, and the cyclosporin dose was slightly tapered to 50 mg twice daily. Furthermore, lamivudine was excluded from therapy on the grounds that it may cause adverse reactions like peripheral neuropathy, dizziness, insomnia and other sleep disorders, as well as depression (especially when administered in combination).

Additionally, the patient had a mild amylase elevation, which may be an adverse reaction of lamivudine.

TABLE 1
LABORATORY FINDINGS

Se	60 mm/h
Leukocyte count	$7.04 \times 10^9/L$
Erythrocytes	$3.55 \times 10^{12}/L$
Hemoglobin	100.0 g/L
Haematocrit	0.29%
MCV	81.6 fl
asalphaPlatelet count	$153 \times 10^9/L$
Creatinine	292 mmol/L
Urea	19.1 mmol/L
Uric acid	599 mmol/L
Glucose	4.7 mmol/L
Total cholesterol	6.0 mmol/L
Tryglicerids	2.4 mmol/L
Na	137 mmol/L
K	3.7 mmol/L
Cl	103 mmol/L
Ca	2.9 mmol/L
P	1.19 mmol/L
Mg	0.81 mmol/L
Bilirubine	8.3 mmol/L
AST	25 U/L
ALT	12 U/L
GGT	20.1 U/L
LDH	416 U/L
CK	594 U/L
Prothrombin time	16 s
INR	1.2
APTV	28 s
Fibrinogen	5.0 g/L
Total proteins	64.0 g/L
Serum amylase	340 U/L

TABLE 2
LUMBAR PUNCTURE FINDING

WBC	$6/mm^3$
RBC	$8/mm^3$
Glucose	2.68 mmol/L
Protein	0.58 g/L

After being discharged from the hospital, the patient's condition improved; she slept better and her walk was more stable. Due to the development of toxic hepatitis in the next month, carbamazepine had to be gradually excluded as well, leading to an improvement of hepatic function in the next six months.

Two years later control MRI showed extensive atrophy of the parenchyma in the frontal and, to a lesser extent, in the parietal regions with widened deep sulci. There were no new lesions in the remaining white matter compared to the previous MRI findings (Figure 2).

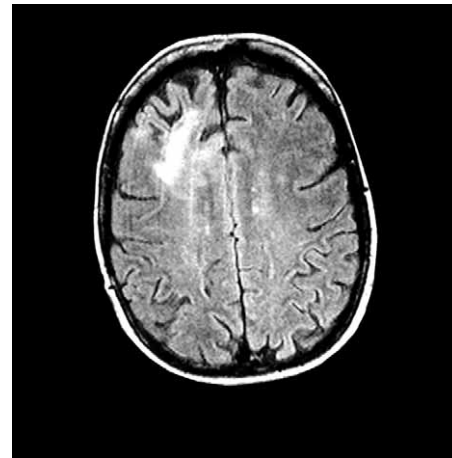


Fig. 2. After two years, control radiological finding of brain MRI: Extensive atrophy of parenchyma was found in frontal and in lesser extent in parietal regions with widened deep sulci.

In the follow up period of five years, she has shown no more epileptic attacks (or other neurological disorders) except for some psychomotorical slowness.

Discussion

Progressive multifocal leukoencephalopathy (PML) usually occurs in an immunocompromised individual, putatively attributable to reactivation of a latent JC virus.

The onset of PML may be insidious. Presenting signs and symptoms include impaired speech, memory loss, changes in mentation, and visual disturbance. Visual field loss (homonymous hemianopsia) and motor weakness, progressing to hemiparesis, are common findings⁵. Patients remain afebrile during the course of the illness. The cerebrospinal fluid is virtually always normal, although there may be a slight elevation in the protein level or cell count.

Our patient showed similar neurological symptoms which we believed were related to the effects of immunosuppressive therapy (cyclosporin, micophenolate mofetil and prednisolon), as well as possibly of lamivudine, in the conditions of the chronic viral infection.

The host and viral factors that lead to the development of PML are not clearly understood. Over 70 percent of adults carry antibodies to JC virus, and JC virus has been shown to persist in kidneys and to be shed in urine². JC virus is a polyomavirus. It was first isolated in 1971, when brain tissue from a patient with PML was inoculated into cell culture derived from a fetal brain⁶. The pathogenesis of infection is unclear, but the virus probably enters the body through the respiratory tract. JC virus appears to target the kidneys as the main site of infection and remains latent for the lifetime of the individual^{5,7}. Reactivation, leading to PML, occurs in immunocompromised individuals. Recent studies indicate that the presence of JC virus in cerebrospinal fluid, as identified by the polymerase chain reaction (PCR), has high specificity for the diagnosis of active disease^{8,9}.

In our patient genome detection of polyomavirus JS from cerebrospinal liquor (PCR) was found negative, therefore the diagnosis of PML was not probable. A definitive diagnosis of PML is made by brain biopsy, but our patient did not agree to this procedure.

Some authors believe that PML should be considered as one of the possible extrahepatic manifestations of HCV infection¹⁰. Furthermore, some earlier sources state that progressive dementia, with or without focal abnormalities or seizures, may be related to progressive multifocal leukoencephalopathy due to infections with other viruses, including herpes simplex virus, CMV, and EBV; and occasionally to demyelination or other toxic effects of cyclosporine or tacrolimus¹¹. There is a report of cyclosporin neurotoxicity after doxorubicin chemotherapy for lymphoproliferative disease after transplantation¹². In this case the authors proposed that an impaired blood-brain barrier from long-term use of cyclosporin enabled doxorubicin to produce neurotoxicity. Some authors suggested that, despite normal concentrations of cyclosporin, its metabolism may have been affected by a concomitant high dose chemotherapy (as evidenced by a raised alanine aminotransferase concentration), leading to the accumulation of toxic metabolites; these could damage the blood-brain barrier and cause neurotoxicity¹³.

The clinical and radiological features of cyclosporin neurotoxicity after chemotherapy are consistent with the posterior leukoencephalopathy syndrome. The reversible posterior leukoencephalopathy syndrome is associated

with headaches, vomiting, confusion, seizures, visual disturbance, and motor signs, in various degrees. Neuroimaging typically shows bilateral, often strikingly symmetrical, white matter changes in the posterior regions of the cerebral hemispheres, particularly the occipital lobes and the posterior parietal lobes. The clinical and radiological findings usually resolve within two to three weeks if the underlying cause is removed¹⁴.

Neuroradiological findings in our patient may fit this syndrome only partially.

Conclusions

Five years later, after the appearance of first neurological disorders, the patient is stable, with normal neurological status and no progression on MRI brain examination. There was a deterioration of renal function after the reduction of immunosuppression, and she began haemodialysis treatment.

There are no previous reports of neurotoxicity associated with hepatitis B and C viruses and the type of chemotherapy regimen that our patient used. Consequently, we started from the assumption that the concomitant use of cyclosporin with mycophenolate mofetil and lamivudine, despite normal concentrations of cyclosporin, might cause the accumulation of toxic metabolites and lead to neurotoxicity that mimics PML in a chronic viral environment.

REFERENCES

1. ASTROM KE, MANCALL EL, RICHARDSON EP JR. *Brain*, 81 (1958) 93. — 2. GREENLEE JE. Polyomavirus. In: RICHMAN DD, WHITLEY RJ, HAYDEN FG (Eds), *Clinical virology* (Churchill Livingstone, New York, 1997) 549. — 3. BERGER JR, SCOTT G, ALBRECHT J, BELMAN AL, TORNATORE C, MAJOR EO, *AIDS*, 6 (1992) 837. — 4. MARK AS, ATLAS SW, *Radiology*, 173 (1989) 517. — 5. MAJOR EO, AMEMIYA K, TORNATORE CS, HOUFF SA, BERGER JR, *Clin Microbiol Rev*, 5 (1992) 49. — 6. PADGETT BL, ZURHEIN G, WALKER D, ECHORODE R, DESSEL B, *Lancet*, 1 (1997) 1257. — 7. GALLIA GL, HOUFF SA, MAJOR EO, KHALILI K, *J Infect Dis*, 176 (1997) 1603. — 8. GREEN-

LEE JE, *N Engl J Med*, 338 (1998) 1378. — 9. HALL CD, DAFNI U, SIMPSON D, CLIFFORD D, WETHERILL PE, COHEN B, *N Engl J Med*, 336 (1998) 1345. — 10. HOOGENRAAD TU, JANSEN GH, VAN HATTUM J, *Ann Intern Med*, 125 (1996) 345. — 11. HOOPER DC, PRUITT AA, RUBIN RH, *Medicine* (Baltimore), 1982). — 12. BARBUI T, RAMBALDI A, PARENZAN L, ZUCCHELLI M, PERICO N, REMUZZI G, *Lancet*, 339 (1992) 1421. — 13. LUCEY MR, KOLARS JC, MERION RM, CAMPBELL DA, ALDRICH M, WATKINS PB, *Lancet*, 335 (1990) 11. — 14. HINCHEY J, CHAVES C, APPIGNANI B, BREEN J, PAO L, WANG A, *N Engl J Med*, 334 (1996) 494.

M. Matijaca

Department of Neurology, University Hospital Split, Spinčićeva 1, 21000 Split, Croatia
e-mail: meri.matijaca@st.htnet.hr

NEUROTOKSIČNOST KOJA OPONAŠA PROGRESIVNU MULTIFOKALNU LEUKOENCEFALOPATIJU U BOLESNICE S TRANSPLANTIRANIM BUBREGOM

S A Ž E T A K

Prikazali smo 55 godina staru bolesnicu kojoj je u tri navrata urađena transplantacija bubrega. Uz imunosupresivnu terapiju, liječena je lamivudinom zbog hepatitisa B i C. Devet godina nakon posljednje transplantacije, bolesnica je postala smetena i konfuzna, a potom je dobila epileptički napadaj tipa grand mal. Nalaz MR mozga je pokazao velike ovalne zone hiperintenzivne u T2 mjerenom vremenu i hipointenzivne u T1 mjerenom vremenu oko frontalnih rogova lateralnih moždanih komora obostrano, te u cerebelarnim hemisferama. Ubrzo nakon smanjenja imunosupresije i isključenja lamivudina iz terapije, bolesnica se neurološki stabilizirala i u razdoblju od sljedećih pet godina nije imala epileptičkih napadaja. Ovakav klinički tijek može se objasniti pretpostavkom da je istovremena primjena imunosupresiva i lamivudina u uvjetima kronične virusne infekcije, uzrokovala nakupljanje toksičnih metabolita i izazvala neurotoksičnost koja sličí progresivnoj multifokalnoj leukoencefalopatiji.