Exp Oncol 2020
42, 3, 238–241

CASE REPORTS

Experimental ONCOLOGY

PROGRESSIVE MULTIFOCAL ENCEPHALOPATHY IN A PATIENT WITH NON-HODGKIN FOLLICULAR LYMPHOMA

*I. Trociukas[1, 2, *], A.E. Zirnis[3], L. Beļajeva[1], A. Rivkina[1, 4], S. Lejniece[1, 4]*

[1]Riga Eastern Clinical University Hospital, Riga, LV-1006, Latvia

[2]August Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga LV-1067, Latvia

[3]University of Latvia, Riga LV-1586, Latvia

[4]Riga Stradins University, Riga LV-1039, Latvia

Progressive multifocal leukoencephalopathy (PML) is a rare and often fatal demyelinating disease of the central nervous system caused by John Cunningham virus (JCV). We present a case report of patient with non-Hodgkin follicular lymphoma, who developed PML after hematopoietic stem cell transplantation and rituximab-bendamustine therapy. JCV DNA was proven both in peripheral blood and cerebrospinal fluid. Patient with 4 years history of follicular lymphoma presented with progressing weakness in the right arm and leg and postural instability. Magnetic resonance imaging scans showed bilateral hyperintense lesions in the cerebellum and centrum semiovale consistent with findings in PML. JCV DNA was detected in patient peripheral blood and cerebrospinal fluid by real time polymerase chain reaction assay in CERBA laboratory (France). Human herpes simplex 6 and 7 DNA were also detected in peripheral blood by PCR. Patients condition rapidly deteriorated with *exitus letalis* after 3 months and 2 weeks from onset of symptoms. This case draws attention to risk for developing PML in patients with long-standing hematological malignancies.

***Key Words*: progressive multifocal leukoencephalopathy, rituximab-bendamustine, JC polyomavirus, follicular lymphoma, hematopoietic stem cell transplantation.**

DOI: 10.32471/exp-oncology.2312-8852.vol-42-no-3.15198

Progressive multifocal leukoencephalopathy (PML) is a rare disease with very high mortality. Most commonly it occurs among patients with underlying immunosuppression, particularly, if their cell-mediated immune system has been impaired. It is a demyelinating disease of the central nervous system (CNS), caused by the reactivation of latent John Cunningham virus (JCV) [1]. Virus is transmitted through inhalation or ingestion. Afterwards, latent infection in the uroepithelium cells and hematopoietic cell lineage is established. Generally, at this stage virus is completely asymptomatic and can be latent for indefinite time. However, it has a potential to re-activate during episodes of immunosuppression. When this happens, JCV virus spreads to CNS, where it infects astrocytes and oligodendrocytes, causing lytic infection [2]. Prognosis of the disease varies greatly, depending on the cause of immunosuppression, with observed mortality rate being 12% in the multiple sclerosis patients to reaching even 83% in patients with neoplasms. Lymphoproliferative disease patients make up the great majority of neoplasm group — 94% [3]. The main reason why these patients are in a much higher baseline risk group for developing PML from monoclonal antibodies is due to the already existing immunosuppression that is inherent to the nature of their disease and due to chemotherapy regimens which involve purine analogues and fludarabine [4, 5]. For clinicians, it is very important to be able to recognize the signs of possible PML early, since the prognosis for this group of patients relies almost exclusively on rapid discontinuation of the immunosuppressive therapy.

We would like to present a case of patient with follicular lymphoma, who developed PML after receiving a stem cell transplant and completing rituximab-bendamustine (R-B) therapy. JCV virus DNA was confirmed both in patient cerebrospinal fluid (CSF) and in blood. The use of patient data for writing this case report was approved by the Ethical Committee of Riga Stradiņs University.

Case description. A 53-year-old female was presented with a two-weeks history of dizziness and impaired sensitivity in her right arm and leg at the end of April 2019. She had a history of a non-Hodgkin lymphoma, follicular, Grade 2, stage IIIA, which was confirmed by a lymph node histological investigation in November 2015. Patient received 3 courses of R-CVP and 3 courses R-CHOP protocol (Table). Positron emission tomography scan performed in September 2016 showed a metabolic activity in lymph nodes located in the left groin area which corresponded to Deauville 4. Subsequently, in November 2016, patient received radiotherapy for the involved groin area — total dosage of 36 Gy in 18 fractions. First remission was achieved.

In June 2017, first relapse was observed (computed tomography (CT) scan showed peripheral and abdominal lymphadenopathy) which was treated according to R-DHAP protocol (Table) and yielded positive response. In total, so far patient had received 3 R-CVP, 3 R-CHOP and 3 R-DHAP courses. A control CT/positron emission tomography scan done in October 2017 was

Submitted: March 4, 2020.

*Correspondence: E-mail: ilze.trociukas@gmail.com

Abbreviations used: AIDS – acquired immunodeficiency syndrome; CNS – central nervous system; CSF – cerebrospinal fluid; CT – computed tomography; HHV – human herpesvirus; HSCT – hematopoietic stem cell transplantation; JCV – John Cunningham virus; MRI – magnetic resonance imaging; PCR – polymerase chain reaction; PML – progressive multifocal leukoencephalopathy R-B – rituximab-bendamustine.

negative. It was decided to treat the patient with autologous hematopoietic stem cell transplantation (HSCT). Stem cell mobilization was started in October 2017. Patient received 6-day course of Filgrastim (granulocyte colony stimulating factor) at a dose of 10 μg/kg/day and a total of $3.1 \cdot 10^6$ /kg $CD34^+$ hematopoietic stem cells were collected. In December 2017, patient received R-BEAM (Table) myeloablative conditioning regimen. A total dose of $3.1 \cdot 10^6$ /kg CD34-positive cells was infused. The engraftment was defined as absolute neutrophil count of $> 0.5 \cdot 10^9$/L on the 11th day post-HSCT and platelet count of $> 50 \cdot 10^9$/L on the 13th day post–HSCT. Following the stem cell transplantation, patient twice suffered recurrent severe herpes zoster infections. Human herpesvirus (HHV)-6 and HHV-7 DNA was detected by polymerase chain reaction (PCR) in blood both before and after the HSCT.

Abdominal lymphadenopathy was detected in a control CT-scan done in the August 2018. Early relapse after stem cell transplant and resistance against chemotherapy was confirmed and therapy according to R-B protocol (Table) was initiated. During this time, patient in total received 6 courses of rituximab (375 mg/m^2 i/v) and 12 doses of bendamustine (a decreased dose of 100 mg for the last bendamustine course was given due to thrombocytopenia caused by usual 150 mg dosage).

During the routine check-up at the end of April 2019, patient complained of progressing weakness in the right arm and leg and postural instability. CT scan done to assess the patient response to therapy showed a slight, but positive improvement of the follicular lymphoma to the R-B regimen, with decrease in spleen size and lymph nodes in the abdomen. However, due to the presenting neurological complains, an magnetic resonance imaging (MRI) scan with contrast for the brain was performed.

MRI scan in T2 projection (Fig. 1) revealed bilateral hyperintense lesions in the middle cerebellum peduncles. In the periphery of right cerebellum, another hyperintense lesion was observed which had a cystic component. A smaller lesion could be seen outside the cerebellum in the centrum semiovale region. The initial differential diagnosis was between encephalitis caused by paraneoplastic syndrome or PML. Upon receiving these results, patient was admitted for further examination.

Results of investigation. Upon arrival in the hospital in the middle of May 2019, neurological investigation was done. It showed slightly impaired speech, weakness in right leg/arm and postural instability which corresponded to the damage of the right side of cerebellum seen in the MRI. Biochemistry results showed only slightly increased ALAT of 47 U/L. Blood analysis showed mild neutropenia of $1.95 \cdot 10^9$/L, lymphopenia of $0.62 \cdot 10^9$/L and thrombocytopenia of $80 \cdot 10^9$/L.

A lumbar puncture with intrathecal dexamethasone injection was performed. A polymerase chain reaction for the CSF was negative for cytomegalovirus, Epstein — Barr, Herpes Simplex 1 and 2 DNA and enterovirus RNA. CFS flow cytometry also excluded follicular lymphoma expansion into the CNS.

A neurosurgeon team was called and repeated neurological evaluation revealed horizontal nystagmus with rotator component, marked ataxia in the right leg and arm and increased coordination impairment. It was decided not to perform brain biopsy due to the high likelihood of permanent neurological damage, opting instead for repeated MRI and symptomatic therapy.

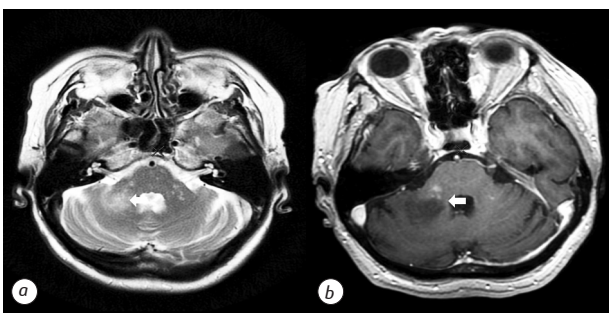

Fig. 1. MRI scan results on 13.05. Hyperintense lesions can be seen on T2 FLAIR bilaterally in the cerebellum peduncles. Lesion in the right peduncle has central cystic component (white arrow). Another contrast-accumulating lesion is located in the frontal lobe. Differential diagnosis can be made between encephalitis with paraneoplastic syndrome or PML with perivascular lymphocytic infiltration: *a* — T2 axial FLAIR; *b* — T1 3D

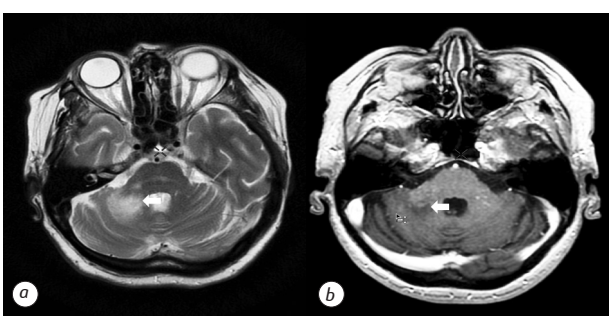

Fig. 2. MRI scan results on 28.05. Lesions in the cerebellum peduncles have become more intense. There is an increase in edema in the right peduncle, with low signal intensity centrally in T1, indicating possible demyelination (white arrow). New multiple lesions in medulla oblongata have appeared, and trident sign can be seen in the pons: *a* — T2 axial FLAIR; *b* — T1 3D

Table. Chemotherapy regimens

R-BEAM	Rituximab 375 mg/m^2 Day –7	Carmustine 300 mg/m^2 Day –6	Etoposide 200 mg/m^2 Days –5 to –2	Cytarabine 200 mg/m^2 Days –5 to –2	Melphalan 140 mg/m^2 Day –1
R-CHOP	Rituximab 375 mg/m^2 Day 1	Cyclophosphamide 750 mg/m^2 Day 2	Vincristine 1.4 mg/m^2 Day 2	Doxorubicin 50 mg/m^2 Day 2	Prednisone 100 mg Days 2–6
R-DHAP	Rituximab 375 mg/m^2 Day 1	Dexamethasone 40 mg Days 1–4	Cytarabine 2000 mg/m^2 Day 3	Cisplatin 100 mg/m^2 Day 1	
R-CVP	Rituximab 375 mg/m^2 Day 1	Cyclophosphamide 1000 mg/m^2 Day 2	Vincristine 2 mg Day 2		
R-B	Rituximab 375 mg/m^2 Day 1	Bendamustine 90 mg/m^2 Days 1 and 2			

Repeated MRI (Fig. 2) at the end of May showed an increased edema in the right middle pedunculi of cerebellum with signs of demyelination in the right part of cerebellum. The existing lesions had not grown bigger but became more intense. New multiple small lesions had appeared on the medulla oblongata and central demyelination of the pons could be seen (trident sign). The lesion in the centrum semiovale remained the same.

PML diagnosis was finally corroborated in June 2019 when CERBA laboratory in France* confirmed the presence of JCV DNA in the patient CSF and peripheral blood (4444 copies/mL) by a real time PCR assay with sensitivity 137 copies/mL. During upcoming 2 months, patient received only symptomatic therapy and her condition continued to deteriorate with *exitus letalis* after 3 months and 2 weeks from the onset of neurological disease.

***Discussion*.** While PML is not a new condition for physicians, with first case described dating already 60 years ago [6], it still is often initially misdiagnosed [3]. As of now, there is no effective treatment available, and the best options are timely discontinuation of monoclonal antibody treatment for autoimmune diseases, giving haematopoietic cell transplant for lymphoproliferative diseases or obtaining immune system reconstitution by antiviral treatment for acquired immunodeficiency syndrome (AIDS) patients [7]. The main goal of these treatments is reducing the existing level of immunosuppression as quickly as possible, but caution must be taken, as there is a possible risk of immune reconstitution inflammatory syndrome. This condition is characterized by clinical deterioration despite regaining at least partial level of immune functions. It is thought to be caused by excessive immune system reaction to virus and is very hard to differentiate from classical PML with inflammatory component [8].

Historically, various hematological malignancies were the most common causes of PML before the AIDS pandemic that started in the 1980s. During the peak of it, the incidence rate of PML in AIDS population reached 7 for 1000 patient years but decreased radically after the advances in the highly active antiviral therapy were made in 1995 [9].

Nowadays, with the appearance of novel immunosuppressive drugs such as monoclonal antibodies (rituximab, natalizumab, efalizumab) [10], reports of PML in human immunodeficiency virus-negative patients, who have been treated with them, are becoming more common [7, 11]. Other known risk factors are stem cell and solid organ transplantation, various chemotherapy regimens such as R-CHOP and glucocorticoids such as prednisone and azathioprine [3]. However, the existing concept that severely compromised cell mediated immune system is a definite prerequisite for development of PML has been challenged in recent reviews in which cases with only transient or mild failure in cellular immunity caused by hepatic cirrhosis, dermatomyositis, chronic kidney failure and other more common clinical conditions were linked with development of PML [12].

In case we presented, patient had a 4-year history of underlying B cell malignancy — low grade follicular non-Hodgkin lymphoma. She had received both complicated chemotherapy regimens and hematopoietic stem cell transplant. PML diagnosis was confirmed according to the Neuroinfectious Disease Section of the American Academy of Neurology proposed criteria. There are 2 main possible routes for confirming PML diagnosis: a) obtaining brain tissue sample and performing neuropathologic demonstration of the typical histopathologic triad (demyelination, bizarre astrocytes, and enlarged oligodendroglial nuclei) coupling it with techniques to detect JCV or as was done in our case b) confirming PML by compatible clinical and radiological findings combining it with detecting JCV DNA in CSF by PCR [13].

According to the retrospective review of 326 various PML cases done by Maas *et al*. [3], median time for onset of PML symptoms after the start of immunosuppressive therapy regimen for neoplasms was 14.2 months. First symptoms for our patient were manifested in April 2019. Patient received first dose of rituximab (as per R-CVP regime) in December, 2015 — 40 months before onset of symptoms. Last R-B therapy was started in September 2018, 8 months before the onset of PML; patient received BEAM regimen and stem cell transplant in December 2017, 16 months prior to first symptoms. Of worth noting are two recurrent episodes of severe herpes zoster infections following the transplantation indicating prominent immunosuppression. There is some evidence of JCV and HHV-6 co-infections in PML patients, however diagnosing it is not easy and DNA PCR testing for brain biopsy sample and hair follicles or nails is recommended to confirm it since HHV-6 DNA is almost never found in CSF for patients with PML [14, 15]. The presence of DNA for HHV-6 and HHV-7 in blood of our patient was confirmed by PCR both before receiving hematopoietic stem cell transplant and after it but since no brain biopsy sample was taken, we can only speculate if they played any role in the pathogenesis of PML.

The initial symptoms — dysarthria and motor weakness — were also found to be the most prevalent in Maas *et al.* [3] study among neoplasms subgroup, with 27% and 55% respectively. Our patient did not show any cognitive deficits, which are found in 49.4% of cases. On the MRI, the lesions were predominantly located in the infratentorial region, which is rare for neoplasms (21.7%). Supratentorial involvement can be seen in 93.4% of cases and our patient had a smaller lesion in centrum semiovale as well. Prognosis for this group is unfavourable, with mortality rates of 83.3% and median survival time of 3.9 months. Our patient had *exitus letalis* after 3 months and 2 weeks from the onset of first PML symptoms [3].

In conclusion, there is a much of what we do not yet know of JCV reactivation. Our patient had re-

*7/11 rue de l'Equerre – Parc d'activité "les Béthunes" 95310 Saint Ouen L'aumone.

ceived various immunosuppression regimes that also included rituximab for years till the PML struck. The days when this diagnosis was primarily confined to the human immunodeficiency virus/AIDS patients are long gone and with more widespread use of various immune system suppressing drugs the amount of cases are expected to rise. Since no specific treatment exists, rapid discontinuation of immunosuppressive therapy is still the best treatment choice so early PML detection is of paramount importance. If neurological symptoms appear in immunosuppressive lymphoma patient, PML may be a possible cause.

REFERENCES

1. **Major EO, Yousry TA, Clifford DB.** Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. Lancet Neurol 2018; **17**: 467–80.

2. **Frohman EM, Monaco MC, Remington G, *et al.*** JC virus in CD34+ and CD19+ cells in patients with multiple sclerosis treated with natalizumab. JAMA Neurology 2014; **71:** 596–602.

3. **Maas RPPW, Muller-Hansma AHG, Esselink RAJ, *et al.*** Drug-associated progressive multifocal leukoencephalopathy: a clinical, radiological, and cerebrospinal fluid analysis of 326 cases. J Neurol 2016; **263**: 2004–21.

4. **Garcia-Suarez J, Miguel D, Krsnik I, *et al.*** Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. Am J Hematol 2005; **80**: 271–81.

5. **Cid J, Revilla M, Cervera A, *et al.*** Progressive multifocal leukoencephalopathy following oral fludarabine treatment with chronic lymphocytic leukemia. Ann Haematol 2000; **9**: 391–5.

6. **Åström KE, Mancall EL, Richardson EP.** Progressive multifocal leuko-encephalopathy: a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. Brain 1958, **81:** 93–111.

7. **Carson KR, Newsome SD, Kim EJ, *et al.*** Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: A report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. Cancer 2014; **120**: 2464–71.

8. **Wattjes MP, Wijburg MT, van Eijk J, *et al.*** Dutch-Belgian Natalizumab-associated PML study group. Inflammatory natalizumab-associated PML: baseline characteristics, lesion evolution and relation with PML-IRIS. J Neurol Neurosurg Psychiatry 2018; **89**: 535–41.

9. **d'Armnio Monforte A, Cinque P, Mocroft A, *et al.*** Changing incidence of central nervous system diseases in the EuroSIDA cohort. Ann Neurol 2004; **55**: 320–8.

10. **Keene DL, Legare C, Taylor E, *et al.*** Monoclonal antibodies and progressive multifocal leukoencephalopathy. Can J Neurol Sci 2011; **38**: 565–71.

11. **Carson KR, Evens AM, Richey EA, *et al.*** Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the research on adverse drug events and reports project. Blood 2009; **113**: 4834–40.

12. **Gheuens S, Pierone G, Peeters P, *et al.*** Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression. J Neurol Neurosurg Psychiatry 2010; **81**: 247–54.

13. **Berger JR, Aksamit AJ, Clifford DB, *et al.*** PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. Neurology 2013; **80**: 1430–8.

14. **Pasca M, Picchioni A, Mazzeo S, *et al.*** A case of recurrent progressive multifocal leukoencephalopathy after human stem cell transplant, with detection of John Cunningham virus and human herpesvirus 6 on cerebrospinal fluid, treated with Mitrazapin, Olanzapin and Foscarnet. Intractable Rare Dis Res 2019; **8**: 275–8.

15. **Nakamichi K, Inoue N, Shimokawa T, *et al.*** Detection of human herpesviruses in the cerebrospinal fluid from patients diagnosed with or suspected of having progressive multifocal leukoencephalopathy. BMC Neurol 2013; **13**: 200.