Progressive multifocal leukoencephalopathy (PML) is a neurological disease caused by infection of the central nervous system (CNS) with the JC polyomavirus (JCV). JCV is endemic and infects a large proportion (70–90%) of healthy individuals worldwide, but infection is latent. JCV reactivation may occur, if the immune function is compromised. Aim: To present a PML case in a CLL patient after a long course of disease and treatment with fludarabine. JCV virus infection in this patient was proven both in brain biopsy material and blood. Methods: Patient with a nine-year history of CLL was hospitalized with the weakness in the right leg and left hand, tremors, speech difficulties. An MRI diagnosed infiltrative glial tumor of the left hemisphere, proliferating predominantly in the frontal lobe, more in the gyrus frontalis superior region. CNS tumor biopsy performed. Results: Morphology and immunoprofile of the lesion consistent with progressive multifocal leukoencephalopathy. The material from biopsy was diagnosed as positive for JCV DNA. JCV and HHV-7 genomic sequences were found in patient’s PBL DNA sample. In a plasma DNA sample, only genomic sequences were detected. Conclusion: The present case draws attention to the fact that the use of fludarabine and its combinations in CLL therapy increases the risk of JCV infection reactivation and development of serious complications like PML.

**Key Words:** progressive multifocal leukoencephalopathy, JC polyomavirus, chronic lymphocytic leukemia, fludarabine, immunosuppression.
clumsiness and a slight slur. The neurologist’s final conclusion was corticomedullary failure of the right side with central paresis of the left arm with tremor, central paresis of the right leg, and motor aphasia. An MRI diagnosed infiltrative gliar tumor of the left hemisphere, proliferating predominantly in the frontal lobe, more in the gyrus frontalis superior region. The process was spreading to the frontal part of corpus callosum and putamen, and also the temporal lobe of the same hemisphere. Several tiny periventricular and hyperintense subcortical vascular foci of the same nature in both hemispheres.

**RESULTS**

Morphology and immunoprofile of the lesion consistent with progressive multifocal leukoencephalopathy (Figure).

**Figure.** Scattered throughout the hypercellular lesion with numerous foamy macrophages and reactive astrocytes there are homogenous intranuclear inclusions in oligodendrocytes with simultaneous ground glass appearance of nuclei (H&E x 40).

The material was additionally examined to detect JCV DNA. DNA was extracted from 107 µm-thick sections obtained from formalin-fixed and paraffin embedded brain tissue. Sections were digested with protease K and DNA was purified on silica columns (Qiagen GmbH, Germany) according to the manufacturer’s protocol. The technique consisted of genomic amplification (nested PCR with JC1/JC2 primers in external amplification and PEP1/PEP2 in internal amplification) followed by restriction fragment length polymorphism with the enzyme BamH1. Beta-globin gene was used as a control for the integrity of the genome of the sample. After amplification with the primers, a 173 bp fragment of the JCV genome was obtained. This fragment was digested with the enzyme BamH1. The reaction mixture was electrophoresed on a 3% agarose gel. The viral subtype was determined according to the digestion bands as described previously [10]. After digestion with the enzyme BamH1 the 173 pb band disappeared and the case was diagnosed as positive for JCV DNA.

JCV was detected in the patient’s blood. The nested polymerase chain reaction (nPCR) was used for the detection of viral sequences in DNA isolated from peripheral blood leukocytes (PBL) and plasma (markers of latent/persistent and active infection, respectively). JCV and HHV-7 genomic sequences were found in patient’s PBL DNA sample. In a plasma DNA sample, only genomic sequences were detected.

JCV causing PML in the patient was confirmed both in brain biopsy and blood. Motor aphasia, hemisindrome of the left side progressed. Patient received symptomatic therapy and died a month after operation, in April 2008. Post-mortem examination was not performed.

**DISCUSSION**

PML was first described in patients with CLL and Hodgkin lymphoma in 1958 [6]. Association between purine nucleoside analogues and PML has been explored in a systematic study of evaluation the clinical characteristics of HIV-negative patients affected by lymphoproliferative disorders (LPD) who develop PML [2]. In this study B-cell CLL was the most frequent underlying LPD and the most frequent treatment received was purine analogues.

In the majority of previously described CLL cases PML diagnosis was confirmed with JCV detection in brain biopsy [2, 7, 8], in some cases JCV was detected in spinal fluid [9, 10]. In most of reported cases, similarly to the patient described by us, PML developed following fludarabine therapy [3, 8, 9, 10], therefore it is considered that the immunosuppressive effect of this therapy may cause JCV activation. Moreover, the case of PML development in 60-year-old male with CLL after 6 months of fludarabine therapy and without JCV infection is previously reported and authors suggested the possible role of fludarabine in producing PML-like lesions in patients with CLL [10]. Another investigation suggests that immunosuppression caused by chronic lymphoproliferative malignancies alone may be a factor in the development of PML and chemotherapy with fludarabine may act as an additional trigger [9], besides some reported cases date back to the time before fludarabine was accessible for treatment [11, 12].

The present case, in addition to the previously reported, draws attention to the fact that the use of fludarabine and its combinations in CLL therapy increases the risk of JCV infection reactivation and development of serious complications like PML. Because development of PML is tightly linked to suppression and/or modulation of the immune system as in development of hematological malignancies as in monoclonal
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antibody treatments, further scrutiny of the course of JCV infection in immune cells will be essential to our understanding of development of PML and identification of new therapeutic targets [13]. The present case, in addition to a few previously reported, draws attention to the fact that the use of fludarabine and its combinations in CLL therapy increases the risk of serious infection complications like PML.

REFERENCES