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Case report/ Kazuistyka

Rituximab-associated progressive multifocal leukoencephalopathy after a single cycle of R-CHOP for T-cell/histiocyte-rich large B-cell lymphoma

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a disease of immunocompromised patients caused by reactivation of the John Cunningham polyomavirus (JCV). A monoclonal anti-CD20 antibody rituximab is widely used as an important part of therapy for B-cell non-Hodgkin lymphomas and various autoimmune diseases. It is not fully explained how rituximab reactivates JCV.

In this report, we present the case of a 61-year-old man with T-cell/histiocyte-rich large B-cell lymphoma who was treated with R-CHOP and intrathecal methotrexate. Two weeks after the first R-CHOP course he developed dysarthria, diplopia, and disturbances in motor coordination. Based on CT/MRI results showing 3 cm × 2 cm large hypodense white matter lesion in left cerebellar hemisphere, and detection of JCV in the cerebrospinal fluid (14 300 viral copies/mL), the patient was diagnosed with PML. Despite treatment attempt with cidofovir and IVIG, the patient's neurological status continued to worsen. He developed progressive motor neuron deficits but retained intact cognitive functions. The patient deceased nearly three months after onset of rituximab treatment.

Rituximab is a milestone in treatment of many hematological and autoimmune diseases. Considering how widespread has the use of rituximab become, the overall risk of developing PML is relatively low. Nevertheless, since the end of 1990s several reports were published on PML development in association with usage of rituximab. The authors would like to emphasize that although the total risk of PML occurrence in patients treated with rituximab is low, it is important that physicians administrating rituximab therapy are aware of this serious complication.

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare, albeit often fatal, central nervous system (CNS) demyelinating disorder caused by reactivation of a latent John Cunningham polyomavirus (JCV) [1–3]. The disease was first described in 1950s by a Swedish neuropathologist Karl-Erik Åström as a complication occurring in patients with chronic lymphocytic leukemia (CLL) and Hodgkin lymphoma [1]. Primary JCV infection is usually asymptomatic and occurs in school age. After that, the virus is latent in 70–90% of the adult population [2]. Latent JCV can be found in kidney epithelial cells, CD34+ hematopoietic cells and possibly early B-cell precursors [4]. It was proposed that hematopoietic stem cells, which carry JCV, can act as Trojan horses and thus enable the virus to pass the blood-brain barrier. During the active phase of the PML, JCV particles are replicated in oligodendrocytes. The virus induces then destruction of myelin sheath and cell death [2].

PML is usually associated with a decreased T-cell response, and it was very infrequent disease until the time of HIV-epidemics in the 1980s [5]. The incidence of PML increased 50 times between 1979 and 1994, but then it has decreased gradually due to the introduction of antiviral treatment of HIV infection.

The rate of PML progression may initially be slow, making the disease difficult to diagnose. Patients present gradual worsening of cognitive functions, speech and vision [1, 2]. Symptoms become more prominent with time, and patients develop motor neuron deficits and ataxia. With disease progression, neurologic deficits accelerate with occurrence of dementia, blindness, pareses, followed by coma and decease. PML diagnosis is confirmed by JCV detection by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF) [2]. Magnetic resonance imaging (MRI) demonstrates typical pictures of multifocal asymmetrical white matter lesions, located in cerebral hemispheres and less often in cerebellum or brain stem. Diagnosis can also be obtained through biopsy, with histopathological analysis of the tissue and complementary immunohistochemical stains (Table I) [2, 6].

Rituximab is a monoclonal anti-CD20 antibody used for treatment of many types of CD20-positive non-Hodgkin lymphomas (NHLs) including CLL [2]. It is also successfully used in autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Expression of CD20 antigen is observed on both healthy and malignant B-cells, but not on hematopoietic stem cells. Rituximab produces a rapid and almost complete clearance of B-cells from peripheral blood, with the effect persisting up to 12 months after completed therapy [7].

Case presentation

A 61-year-old previously healthy Swedish man with a periodical alcohol abuse, presented with a three-months-long history of diffuse abdominal pain, tiredness and weight loss. Computed tomography (CT) imaging revealed abdominal and thoracic lymphadenopathy at multiple sites as well as prominent splenomegaly. Lymph node biopsy disclosed infiltration of T-cell/histiocyte-rich large B-cell lymphoma. The patient was scheduled for 6 courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) at 14-day intervals and intrathecal methotrexate. He was also found to have undergone hepatitis B, and treatment with lamivudin (Zeffix™) was initiated.

Two weeks after the first R-CHOP-14 course the patient came for a follow-up visit and evaluation before the next treatment course. He presented dysarthria and reported experiencing diplopia, disturbances in motor coordination and loss of large muscle group strength for several days before. Lymphoma therapy was postponed and the patient was admitted to the department of neurology. Brain CT was performed on the same day, and revealed the presence of 3 cm × 2 cm large hypodense white matter lesion in left cerebellar hemisphere as well as numerous nonspecific white matter lesions. These findings were later confirmed by MRI and tentative radiological diagnosis was lymphoma or PML or low grade tumor. Lumbar puncture was performed, with extensive examination for potential infectious agents. The initial assessment suggested CNS involvement by lymphoma since only one major lesion was detected and its location was atypical for PML.

Results of JCV-PCR analysis in the CSF sample were received 3 weeks after initiation of the first R-CHOP-14 course, demonstrating 14 300 viral copies/mL (Fig. 1). Other assays failed to reveal any bacteria, virus or fungal infection. A brain biopsy was discussed with neurosurgeons, but they advised against biopsy as clear signs of PML were already identified.

The patient's clinical status has gradually improved, and 4 weeks after R-CHOP treatment onset he was in neurologically nearly normal condition apart from minor problems with his body balance. At that time, the number of

Table I – Diagnostic signs and symptoms of progressive multifocal leukoencephalopathy

Clinical findings	Rapidly progressing neurological deficits and worsening of motor neuron functions; usually cognitive defect and impaired field of vision
Histopathology of brain tissue (if biopsy performed)	Characteristic histopathological findings [7]: • Demyelinisation • Bizarre astrocytes • Enlarged oligodendroglial cell nuclei • JCV demonstrated by immunohistochemical stain or in electron microscopy
Laboratory findings	Detection of JCV in CSF by means of PCR
Radiological findings	MRI or CT (with contrast) shows multifocal white matter lesions with no or only discrete contrast enhancement

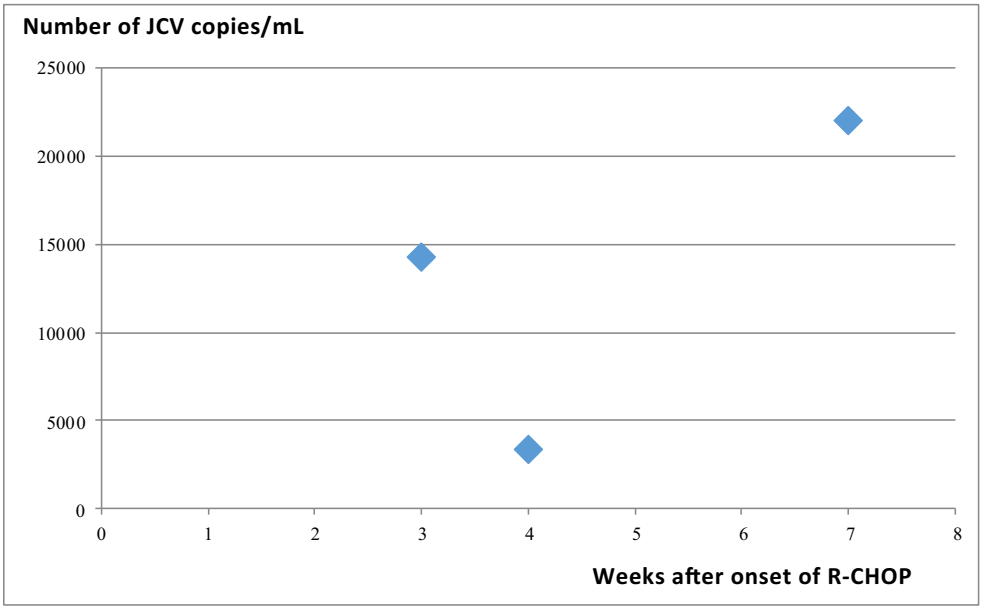

Fig. 1 – Changes in patient's JCV levels in cerebrospinal fluid samples over time

JCV copies in CSF clearly decreased to 3400 copies/mL (Fig. 1). New brain MRI scans taken on the same day revealed though a new band-like lesion with contrast enhancement in proximity to the already known lesion in the left cerebellum hemisphere.

Four weeks after onset of the first R-CHOP course the patient received another one, but this time only CHOP without rituximab due to suspected PML. No intrathecal methotrexate was given. He was discharged home, with planned follow-up visit at the outpatient clinic two weeks later. However, he did not show up to the appointment, and did not answer phone calls.

A couple of days later he presented to the emergency department with newly appearing neurological symptoms and inability to walk. Clinical examination revealed dysarthria, decreased strength in large muscle groups and decreased fine motor neuron function on the left side, with positive Babinski sign on the left, involuntary movements and inability to stand still.

Acute MRI of the brain was ordered, with suspicion of rapid PML progression. That was confirmed on MRI scans, with new lesions appearing in the upper part of medulla oblongata and pons. The previously described big lesion in cerebellum has further increased in size, with apparent cystic degeneration and necrosis. New lesions appeared in the right parietal lobe. Multiple plaque-like white matter lesions were still visible. Contrast enhancement was very discrete, a feature characteristic for the PML (Fig. 2). Radiological and clinical findings pointed clearly to PML, with progression since the first diagnosis.

The patient has received cidofovir (5 mg/kg i.v.) twice, as well as two doses of intravenous immunoglobulin (IVIG). At the time of hospital admission number of JCV copies in CSF increased to 22 200 copies/mL (*i.e.*, approx. 7 weeks after initiation of R-CHOP therapy) (Fig. 1). CT scans of thorax and abdomen revealed slight reduction in size of the enlarged lymph nodes as compared to the status before the first R-CHOP course. Fearing that PML can further progress, a decision was made to abstain from intensive immunochemotherapy, and the patient was given a single dose intravenous vincristine (Oncovin™).

Unfortunately, the patient's clinical condition continued to worsen. He developed progressive motor neuron deficits but retained intact cognitive functions. The patient demonstrated difficulties in swallowing, was unable to speak, and experienced significant problems due to mucus accumulation in the respiratory tract in course of an infection for which he was given broad spectrum antibiotics. A total parenteral nutrition was started as he could not swallow without the risk of aspiration into airways.

Three months after the first R-CHOP course the discussion was commenced on the possibility of therapy with T-cells specific against JCV and patient's siblings were HLA-typed. Moreover, experimental usage of interleukin 7 (IL-7) in patient was discussed. However, this was considered as pointless as the patient's lymphoma was not in remission, and more intensive treatment would be required which would further aggravate the patient's PML. JCV specific T-cell therapy was also abandoned as the patient's status was deemed not compatible with the study prerequisites, which among others included performing a positron emission tomography before infusion of T-cells. The patient's neurological status continued to worsen, and he deceased nearly three months after the administration of rituximab treatment.

During the course of patient's care, a report was sent to the Swedish Medical Products Agency (Läkemedelsverket) concerning PML as a suspected adverse event of therapy with MabThera™ (rituximab), and a notice was sent to the drug producer, a pharmaceutical company F. Hoffman-La

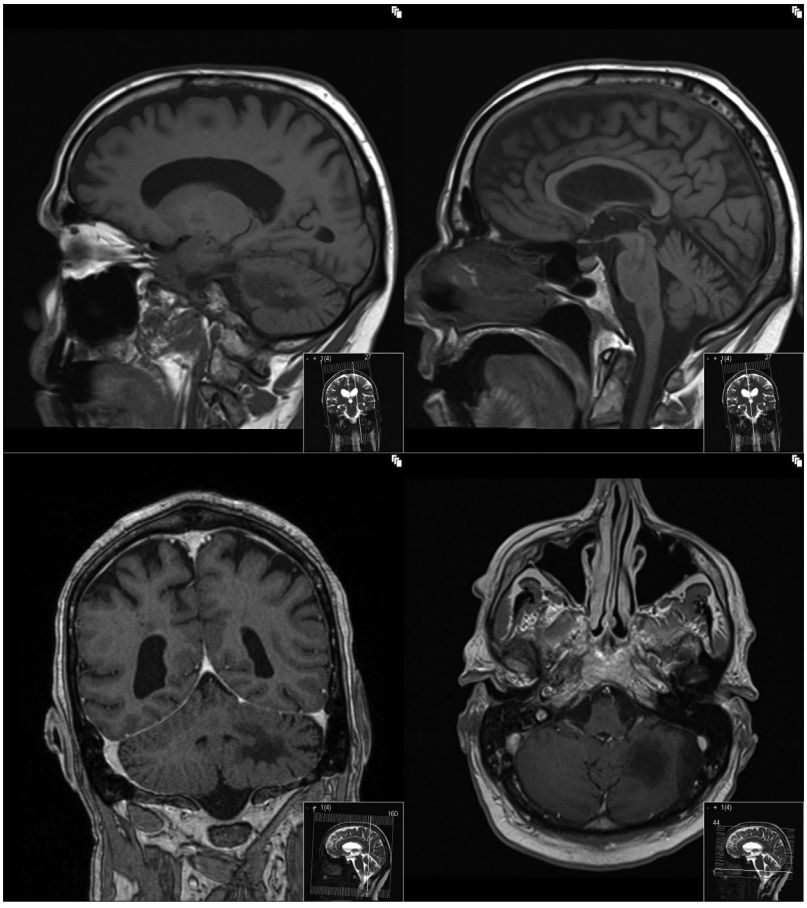

Fig. 2 – MRI scans of patient's brain with widespread PML lesions in left cerebellar hemisphere, medulla oblongata, and pons

Roche Ltd. The Agency replied that a relationship can be implied between usage of the medical agent MabThera™ and the adverse event of PML occurrence. The Agency pointed out that cyclophosphamide, doxorubicin and vincristine should also be perceived as other potential causative agents.

Discussion

Monoclonal antibodies have revolutionized treatment of multiple hematological and autoimmune diseases and are currently in widespread use. In Sweden, with a population of approx. 10 million people, almost 2000 new cases of malignant lymphoma are diagnosed each year in adults, most of these representing B-cell NHL with CD20-positivity. Of those, the most common diagnoses include diffuse large B-cell lymphoma, follicular lymphoma and CLL, which constitute two-thirds of all newly diagnosed lymphomas.

PML as a complication of rituximab therapy was first noted in the end of 1990s [2]. Between 1997 and 2008 only, 57 cases of rituximab-associated PML were reported worldwide, including 52 patients with B-cell NHL, 2 patients with SLE, one patient with RA, one patient with idiopathic autoimmune pancytopenia, and one patient with idiopathic thrombocytopenic purpura (ITP) [8]. To the best of our knowledge, only one case of rituximab-associated PML in NHL was reported up till now in Sweden [9]. The case concerned a female patient with a transformed high-grade B-cell NHL.

However, we were not able to identify any Swedish report on rituximab-associated PML in patient with newly diagnosed B-NHL who developed PML after just a single course of rituximab. It is very unusual with such short time between administration of rituximab and the onset of PML, but based on our case, apparently possible. According to the study by Carson et al., median time from the first rituximab dose to diagnosis of PML was 16 months (range 1–90 months) [8]. Noteworthy, median time between the last dose of rituximab and symptomatic JCV viral reactivation was 5.5 months. On average, six doses of rituximab (range 1–28 doses) were administered before PML diagnosis was made, and a median survival time following PML diagnosis was 2 months (range 0.4–122 months) [8].

Possible factors predisposing to a more rapid PML progression include lower CD4+ count (<200 cells/μL; ref.: 500–1600) and onset of PML signs shortly after the last administered rituximab dose (within 3 months) [8, 10]. All the patients who developed PML within 3 months from rituximab infusion died, as compared to 84% patients who developed PML more than 3 months after the last obtained

rituximab dose. In the present case, the CD4+ cell number was not assessed. However, the correlation between a development of PML soon after rituximab infusion and a rapid progression of the disease could be observed.

Currently, there is no effective treatment of PML available [11]. Cytarabine has been tried in most cases but studies on HIV-positive patients with PML did not reveal any beneficial effect of neither intravenous or intrathecal cytarabine on survival [12, 13]. However, several reports demonstrated a certain improvement of PML in HIV-negative patients following intrathecal administration of cytarabine [14]. Other reported treatment attempts included administration of mirtazapine, cidofovir, donor lymphocyte infusion (DLI), IVIG and risperidone [2]. The presented patient unfortunately did not experience any beneficial effect of cidofovir or IVIG.

Mortality in rituximab-associated PML in patients treated for NHL is very high [2, 11, 15]. In the previously mentioned study, Carson et al. reported that 90% patients died due to PML, and all the survivors had persistent neurological symptoms [8]. A slightly better survival was observed in patients who developed PML after stem cell transplantation, either autologous or allogeneic [8, 16]. One can speculate that it may be due to the fact that the transplanted patient has a better ability to recover immune system in the long run.

Rituximab as a trigger of PML

Pathophysiological mechanism behind correlation of rituximab treatment and PML is not well understood. One theory suggests that depletion of mature B-cells following rituximab administration facilitates expansion of pre-B-cells infected with JCV [2]. Studies have shown that B-cell reconstitution after rituximab therapy causes a disproportional increase in immature B-cells [7, 17] but the explanation to this phenomenon is probably more complex.

Patients with ITP who had been administered rituximab had changes in T-cell activity following B-cell depletion [18]. A study done in patients with multiple sclerosis (MS) showed decrease of the total T-cell count in CSF up to 6 months after rituximab administration [19]. Other studies demonstrated however quite an opposite effect of rituximab on T-cell population [20].

Bennett proposed a hypothesis on the role of bone marrow in rituximab-associated PML [4]. His analysis of bone marrow samples showed that all 5 specimens obtained from patients with lymphoma and PML were positive for JCV, compared to only 2 out of 86 bone marrow samples from patients who had lymphoma but not PML. Indeed, JCV remains in latent form in CD34+ hematopoietic stem cells and most likely also in immature B-cells. Chemotherapy mobilizes stem cells from bone marrow and induces quantitative reduction in the T-cell population. According to Bennett's theory rituximab diminishes then the qualitative T-cell response, and progenitor cells bearing latent JCV proliferate following the overall B-cell depletion [4]. However, the hypothesis was based on retrospective findings, and was never laboratory verified.

Occurrence of PML was also observed in untreated patients with lymphomas, it is therefore difficult to assess how much does rituximab itself increase the risk of the disease. An Italian study of 976 patients with NHL demonstrated a significantly higher risk of developing PML in subjects treated with rituximab [21]. It is currently difficult to perform similar studies, as rituximab is a part of standard therapy protocols in B-cell NHLs. Besides, PML occurred after rituximab therapy even in patients not having a lymphoma, *e.g.* in subjects with SLE or RA.

Another issue is the extent to which chemotherapy included in lymphoma treating protocols contributes to immunomodulation and PML development [11, 15]. Carson et al. pointed out that all patients who developed PML had previously received treatments affecting the immune system, including alkylating agents, corticosteroids, purine analogs or immunomodulators for prevention of graft-*versus*-host disease (GvHD) after allogeneic stem cell transplantation [8]. Some of these patients had though been treated with rituximab and steroids but not cytotoxic drugs. Rituximab seems therefore to induce PML even without the context of chemotherapy.

The present patient had not been treated with chemotherapy until administration of R-CHOP, but he had been given high dose cortisone pretreatment for 3 weeks while awaiting definitive histopathological confirmation of NHL. In his case we could not identify an underlying defect in cellular immunity. He developed neurological symptoms already 10 days after receiving first R-CHOP cycle, which points to an unusually rapid disease onset. He improved spontaneously after the first PML symptoms and 14 days later he was in an apparently normal clinical condition, which is different from a known natural PML course. At that time even the number of JCV copies decreased spontaneously in his CSF sample (Fig. 1).

The patient developed next episode of the disease approx. 2–3 weeks following the second CHOP course (this time without rituximab), and JCV titer in CSF was even higher than during the first symptomatic episode. It is unclear why he initially improved but it can be assumed that CHOP treatment without rituximab contributed to PML reactivation. It would be interesting to know if the patient had low titers of CD4+ cells from the beginning, and, if so, was the lymphoma that caused this phenomenon or was there another causative factor. However, a routine infectious work-up was performed at the time of NHL diagnosis, and the patient was found to be HIV-negative.

Other agents that may cause PML

Development of PML can also be induced by monoclonal antibodies other than rituximab [2, 22–25].

Natalizumab is an antibody binding alfa4-integrin on T-cells and it is successfully used in therapy of refractory MS [2, 22]. The first ever case of natalizumab-associated PML was reported in 2005, and the agent was removed from the market. Currently, natalizumab is again in use but only under strict control for occurrence of any PML-symptoms [23, 24]. Mortality in natalizumab-induced PML is markedly lower as compared to cases where rituximab was the trigger [2, 22]. One may speculate if it is because MS patients are in general more immunocompetent than patients with lymphomas.

Efalizumab is an anti-CD11 monoclonal antibody used in treatment of plaque psoriasis. Several cases of efalizumab-associated PML were reported and as a result the antibody was retrieved from market in 2009 and is no longer in use [2, 23].

Other drugs that can possibly induce PML include potent immunosuppressive agents such as tacrolimus or cyclosporine [25].

Conclusions

Rituximab is a milestone in treatment of many hematological and autoimmune diseases. Nevertheless, since the end of 1990s several reports were published on PML development in association with usage of this antibody. Risk of PML has increased with rituximab therapy but considering how widespread has the use of rituximab become, the overall risk of developing PML is relatively low [2, 8].

Further studies are warranted for a better understanding of rituximab interaction with T-cells and its immunomodulatory mechanisms. Ideally, a strategy should be elaborated to identify at an early stage patients at risk of developing PML. Measuring the CD4+ cell count at initiation of rituximab treatment can be of value. During ongoing rituximab therapy a close clinical follow-up is crucial so as to detect any developing neurological signs or symptoms which can point to PML, and the disease should always be included in differential diagnosis.

In the described case clinical suspicion of PML was made early after symptoms onset, and because of this rituximab was withdrawn from therapy protocol. This however did not improve patient's outcome, resulting in decease 3 months after PML symptom onset.

Authors' contributions/ Wkład autorów

MF – assisted in report design, gathered and analyzed the clinical and laboratory data, performed the literature search, drafted the manuscript; MK – gathered and analyzed the laboratory data, drafted the manuscript; MM – planned the report design, gathered and analyzed the clinical and laboratory data, performed the literature search, drafted the manuscript.

Conflict of interest/ Konflikt interesu

None declared.

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None declared.

Ethics/ Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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