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General review

Progressive multifocal leukoencephalopathy in patients receiving rituximab and cyclophosphamide after haplo-identical T-cell replete transplantation and review of the literature

R. Salem [a], R. Massoud [a], S.S. Kanj [b], M. Hamdan [b], R. Salman [c], A. Bazarbachi [a], J. El-Cheikh [a,*]

[a] Bone Marrow Transplantation Program, Department of Internal Medicine, American University of Beirut, Beirut, Lebanon
[b] Infectious Disease, Department of Internal Medicine, American University of Beirut, Beirut, Lebanon
[c] Diagnostic Radiology Department, American University of Beirut, Beirut, Lebanon

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ABSTRACT

John Cunningham virus (JCV) reactivation, occurring mainly in immunocompromised patients, leads to progressive multifocal leukoencephalopathy, an uncommon but lethal disease. JCV reactivation after T-cell replete haploidentical stem cell transplantation, in the pre-cyclophosphamide era, is poorly represented in the literature. We therefore describe two cases of acute myeloid leukemia who developed JCV reactivation after receiving cyclophosphamide and rituximab post haploidentical stem cell transplantation, and review the literature, aiming to a better understanding of the disease course and its risk factors.

1. Introduction

John Cunningham virus (JCV) reactivation occurs essentially in immunocompromised patients and has been described in multiple conditions associated with immunosuppression, such as patients with acquired immunodeficiency syndrome, patients with solid organ or hematologic malignancies receiving chemotherapy, and patients on immunosuppressive treatment after transplant or autoimmune diseases, for instance natalizumab in Crohn's disease [1] or multiple sclerosis [2], and lately rituximab [3]. It subsequently leads to progressive multifocal leukoencephalopathy (PML), an uncommon but lethal disease [4–6].

Mortality occurs in 33–50% of patients with PML, mostly during the first few months following diagnosis, depending on the severity of their underlying disease. A wide range of neurological disabilities was described among survivors. Only a few cases of JCV reactivation in patients who had haploidentical stem cell transplantation (haplo-SCT) were reported in the literature, all in the T-cell replete and pre-cyclophosphamide era.

Therefore, we report two cases of AML, treated at our referral center, who developed JCV reactivation after receiving cyclophosphamide and rituximab post haploidentical-SCT, followed by a review of the literature encompassing the epidemiology, diagnosis and treatment options for this condition.

2. Case 1

We report the development of PML after haplo-SCT in a 64-year-old woman, diagnosed in July 2014 with myelodysplastic syndrome, transformed in January 2015 to acute myeloid leukemia (AML). Molecular studies were negative for NPM1, FLT3, c-KIT and CEBPa, translocation t(15;17), t(9;11),t(8;21), t(9;22), and inversion [16] and who achieved complete remission (CR) confirmed by bone marrow aspirate and flow cytometry. She was initially treated by idarubicin 12 mg/m^2/day for 3 days and continuous infusion of cytarabine 1.5 g/m^2/day for 4 days, complicated by reversible liver toxicity. She then received 5 monthly courses of maintenance 5-azacytidine 75 mg/m^2/day for 7 days every 28 days as a bridge for haplo-SCT. No full match donor was found in her relatives. At the time of transplantation, she was in complete remission (CR) with no organ dysfunction. Conditioning regimen consisted of thiotepa 5 mg/kg on day −7, fludarabine 30 mg/m^2/day for 5 days starting on day −6, intravenous busulfan 130 mg/m^2/day for 2 days starting on day −3 and thymoglobulin

* Corresponding author at: Bone Marrow Transplantation Program, Department of Internal Medicine, American University of Beirut, Medical Center, P.O. Box 113-6044, Beirut, Lebanon
E-mail address: je46@aub.edu.lb (J. El-Cheikh).

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2.5 mg/kg for 2 days starting on day −2. A total CD34+ cell dose of 10.37×10^6/kg was infused on day 0, followed by post-transplant cyclophosphamide 50 mg/kg/day on days 3 and 4, with urometixan. Cyclosporine and mycophenolate mofetyl were given as prophylaxis of graft versus-host disease (GVHD) started on day +5. The donor (her son) shared 3/6 HLA Class I and 2/4 HLA Class II antigens with the patient and had ABO rhesus incompatibility. Neutrophil engraftment ($>0.5 \times 10^9$/L) occurred on day 13. Evaluation of the disease on day 30 and day 100 post haplo-SCT was still consistent with CR, and 98% full donor chimerism. The patient was started on post haplo-SCT maintenance using reduced dose 5-azacytidine (32 mg/m^2/day for 5 days monthly) starting day +47 and received only 2 cycles. On day 53, she had cytomegalovirus (CMV) reactivation detected by quantitative polymerase chain reaction (PCR) in the peripheral blood with 7700 copies, treated by valganciclovir hydrochloride. She then developed Epstein–Barr virus (EBV) reactivation on day 102 detected by PCR in peripheral blood with 14,000 copies/mL treated by weekly rituximab 375 mg/m^2 for 3 doses.

On day +122, she presented to emergency department with myalgia, high grade fever, chills and dry cough. Computerized tomography scan of the chest, abdomen and pelvis did not show any focus of infection and the patient was started on piperacillin-tazobactam and oseltamivir that was stopped when influenza PCR turned out to be negative. However, she had a persistent unexplained fever, along with headache and a true vertigo that started 3 days later. At that time, she was alert, awake and oriented to time, place and person, with a comprehensive speech and normal cranial nerves, motor and reflexes exam. Antibiotics were changed to meropenem and levofloxacin, and voriconazole was added, empirically. A brain magnetic resonance imaging (MRI) on day 125 showed 2 cortical-subcortical foci of abnormal T2 signal in the right superior temporal gyrus and left temporo-parietal lobe consistent with early infectious process (Figs. 1 and 2). Since that, she started to deteriorate rapidly and got transferred to the ICU then intubated on day 133. Investigations showed CMV, EBV and human herpesvirus 6 (HHV6) reactivation in the broncho alveolar lavage (BAL), coagulase-negative *Staphylococcus* and multidrug resistant *Acinetobacter baumanii* bacteremia, simultaneously. Cerebrospinal fluid (CSF) studies for enterovirus, *Toxoplasma*, cysticercosis, *Borrelia*, *Cryptoccocus*, varicella zoster virus (VZV), and herpes simplex virus (HSV) were negative. Blood studies for *Legionella* antigen, parvovirus PCR, and adenovirus PCR were negative. BAL studies for RSV and *Aspergillus* antigen were also negative. Interestingly JCV PCR in CSF was negative on day 132 but positive on day 150 in blood with 490 copies. At that time patient was taking foscarnet treating CMV in addition to the appropriate antibiotic therapies for bacteremias and other bacterial infections (tigecycline and colistin). A repeat MRI of the brain showed multiple strokes, and additional investigations with transesophageal echocardiography showed mild mitral regurgitation, grade ¼, with 2 mobile masses (9 mm × 5 mm each) compatible with vegetations, involving the atrial side of both mitral leaflets at their cooptation zone. The patient rapidly decompensated and died on day 190. Autopsy of the brain for further evaluation was not done in respect for the family's decision.

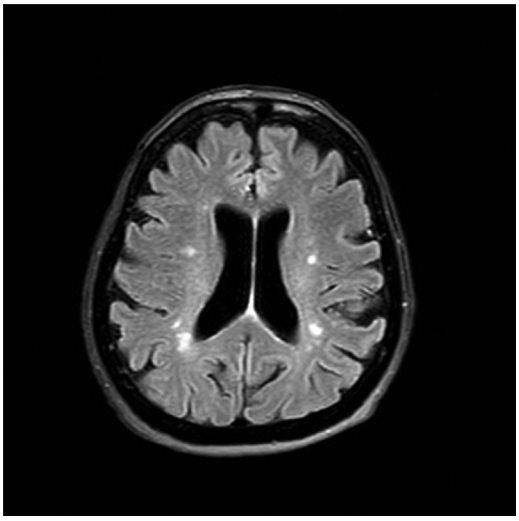

Fig. 1. Axial cuts of brain magnetic resonance imaging (MRI) after gadolinium injection showing two scattered foci of high FLAIR signal in the periventricular cortical-subcortical white matter in favor of early infection process.

3. Case 2

We also report the development of PML after haplo-SCT in a 49-year-old woman, known to have bipolar disorder and diagnosed in April 2015 with AML. Molecular studies were positive for NPM1 and FLT3, negative for c-KIT and CEBPa, translocation t(15;17), t(9;11),t(8;21), t(9;22), and inversion [16], and hyperdiploid karyotype (82-86,XXXX [4]/46,XX [15]). She was initially treated by idarubicin 12 mg/m^2/day for 3 days and continuous infusion of

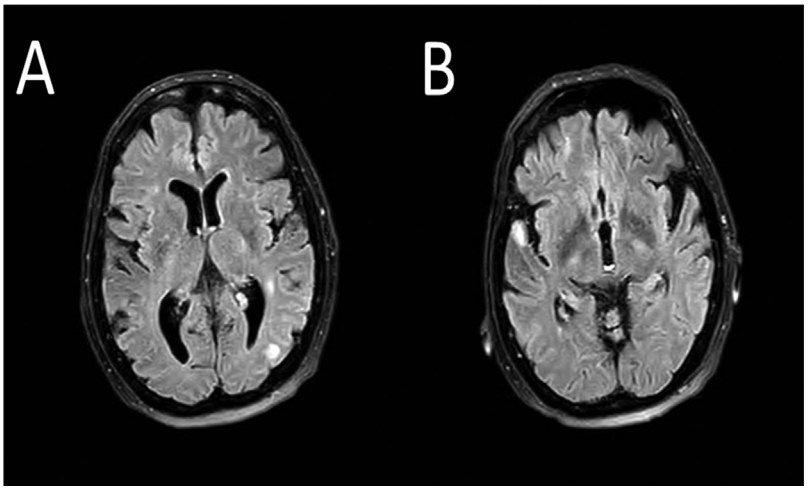

Fig. 2. A and B. Axial cuts of brain MRI after gadolinium injection showing two cortical-subcortical foci of high FLAIR signal in right superior temporal gyrus and left temporo-parietal lobe; an early infectious process should be ruled out.

cytarabine 1.5 g/m^2/day for 4 days, and achieved complete remission (CR) confirmed by bone marrow aspirate and flow cytometry with a normal karyotype. FLT3 PCR became negative, but NPM1 remained positive so sorafenib 400 mg orally twice daily was started with the first consolidation. No full match donor was found among her relatives.

At the time of haplo-SCT, she was in CR with no organ dysfunction, and the conditioning regimen consisted of thiotepa 5 mg/kg on day −7, fludarabine 30 mg/m^2/day for 5 days starting on day −6, intravenous busulfan 130 mg/m^2/day for 2 days starting on day −3 and thymoglobulin 2.5 mg/kg for 2 days starting on day −2. A total CD34+ cell dose of 6.2×10^6/kg was infused on day 0, followed by post-transplant cyclophosphamide 50 mg/kg/day on days 3 and 4, with urometixan. Cyclosporine and mycophenolate mofetyl were given as prophylaxis of GVHD started on day +5. The donor (her son) shared 3/6 HLA Class I and 3/6 HLA Class II antigens with the patient and had ABO rhesus incompatibility. Neutrophil engraftment ($>0.5 \times 10^9$/L) occurred on day 14. Evaluation of the disease on day 30 and day 100 post haplo-SCT was still consistent with CR, negative NPM1 and 99% full donor chimerism. The patient received also weekly rituximab for ABO incompatibility (total of 4 doses) started on day +70 and two sessions of plasmapheresis after completion of rituximab at day +108 and +130 days post haplo-SCT. On day +46, she had CMV reactivation detected by PCR in the peripheral blood with 1580 copies, treated by valganciclovir hydrochloride and made a full recovery on day 200 post haplo. The patient was started on 5-azacytidine (32 mg/m^2/day for 5 days monthly) for persistent molecular disease, discontinued after 2 cycles. She was also started on sorafenib 400 mg twice daily on day +48, discontinued on day +76 due to grade III hematological toxicity, and resumed on day +167.

Thirteen months post haplo-SCT, she presented with left upper and lower limbs weakness. Brain MRI showed abnormal high T2 signal in the premotor cortices and the right thalamus, not restricting on diffusion images, raising the suspicion of PML (Fig. 3). CSF analysis showed polyoma JCV-DNA PCR positive 11 months post haplo-SCT, viral load was 5530. She was started on weekly intravenous immunoglobulins and made progressive improvement. Repeated MRI 3 weeks later, at 1 year post haplo-SCT (Fig. 4) was in favor of progressive multifocal leukoencephalopathy but with improved clinical symptoms. She was switched to intravenous immunoglobulins every 3 weeks on January 2017. She was also started on risperidone on December 2016 with progressive dose escalation with the aim to reach a total daily dose of 8 mg. However, she developed dysarthria on day +21 of risperidone at the dose of 4 mg/day so risperidone was discontinued. The patient continued to improve clinically and by imaging (Fig. 5) and CSF PCR became negative for JC virus 16 months post haplo-SCT. Repeat MRI three months later, 19 months post haplo-SCT showed interval decrease in the abnormal high FLAIR signal and enhancement in the bilateral cortical, subcortical lesions frontal lesions since the previous examination in keeping with improvement (Fig. 6). At her last follow-up, 23 months post haplo-SCT the patient has complete resolution of her clinical symptoms, with good performance status and she still in CR for her AML with negative MRD.

4. Literature review and discussion

JCV, a ubiquitous, neurotropic, double-stranded circular DNA polyomavirus was initially described in 1971. PML was first described as a syndrome by Astrom in 1958, and was later associated with JCV [7]. Exposure to JCV, independently of the clinical syndrome, is detected in up to 90% of adult population [8]. The analysis of the viral protein 1 gene allowed to distinguish eight major genotypes and numerous subtypes of JC virus [9] with a higher prevalence of types I and IV in Europe and in the USA

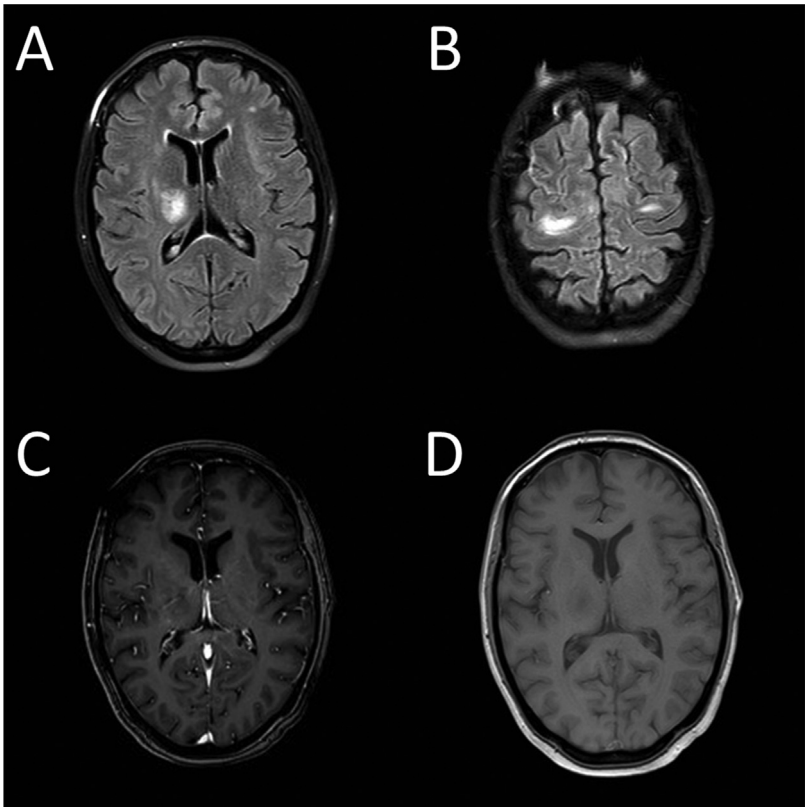

Fig. 3. Axial cuts of brain MRI showing lesions involving the pre-motor cortex bilaterally and the right thalamus showing low signal on T1 (D), high signal intensity on T2 FLAIR (A, B). Mild patchy enhancement involving the right thalamic lesion (C). (A: flair right thalamus; B: flair pre-motor cortex; C: gadolinium; D: T1)

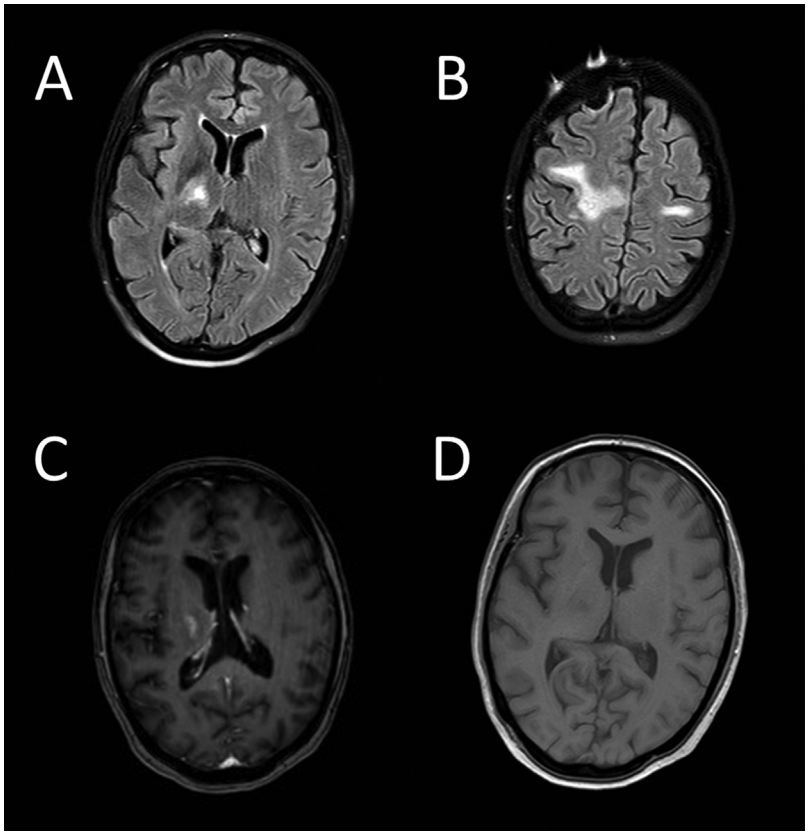

Fig. 4. Axial cuts of brain MRI showing increase in the extent of the previously described abnormal high FLAIR signal lesions (A, B) with increase in their enhancement (C, D). (A: flair right thalamus; B: flair pre-motor cortex; C: gadolinium; D: T1)

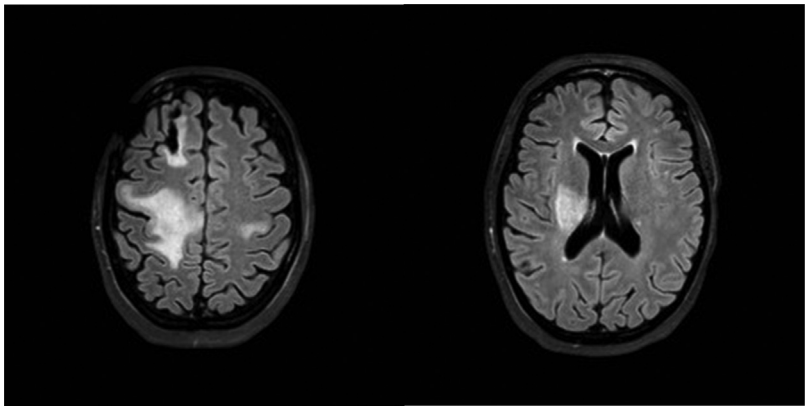

Fig. 5. Axial cuts of brain MRI showing further increase in the extent of the lesions. To note that no gadolinium was administered.

[10–13]. Primary polyomavirus infection is usually asymptomatic and is acquired during childhood most commonly through the upper respiratory tract by inhalation or oral intake [14,15]. After the initial exposure, JCV may persist in a latent state in the kidneys, lungs, monocyte-macrophage cells and B lymphocytes [16,17] and will reactive when an immunosuppressive state develops [18–20].

In the pre-human immunodeficiency virus (HIV) era, PML was rare; in fact, 85% of all PML cases are described in patients with acquired immunodeficiency syndrome (AIDS) [8,21,22]. The use of monoclonal antibodies and novel immunomodulatory therapies for autoimmune diseases, multiple sclerosis, Crohn's disease, non-Hodgkin's lymphoma, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) [23], especially rituximab, exemplifies the role of host immunity suppression in the pathogenesis of PML, as the above situations are also associated with a higher risk of PML [24] (approximately 1/4000 in SLE and 1/25,000 in RA) [25]. Another example is efalizumab which was withdrawn from the market as it induced PML in 1/500 patients with psoriasis [23]. The incidence of PML in the hematopoietic cell transplantation (HCT) population is significantly lower compared to patients with AIDS, with comparative incidence rates of 35.4 vs. 130 per one-hundred thousand person years, respectively [26].

The literature only reports two cases of JCV reactivation post haplo-SCT, one by Focosi et al. in 2006 and one by Pelosini et al. in 2008, with both occurring after T depleted SCT and in the pre-cyclophosphamide post haplo-SCT era [3,27]. In the two cases presented above, rituximab was administered post haplo-SCT for different indications, one to treat EBV reactivation for a total of 3 weekly doses and the other for ABO incompatibility for a total of 4 weekly doses.

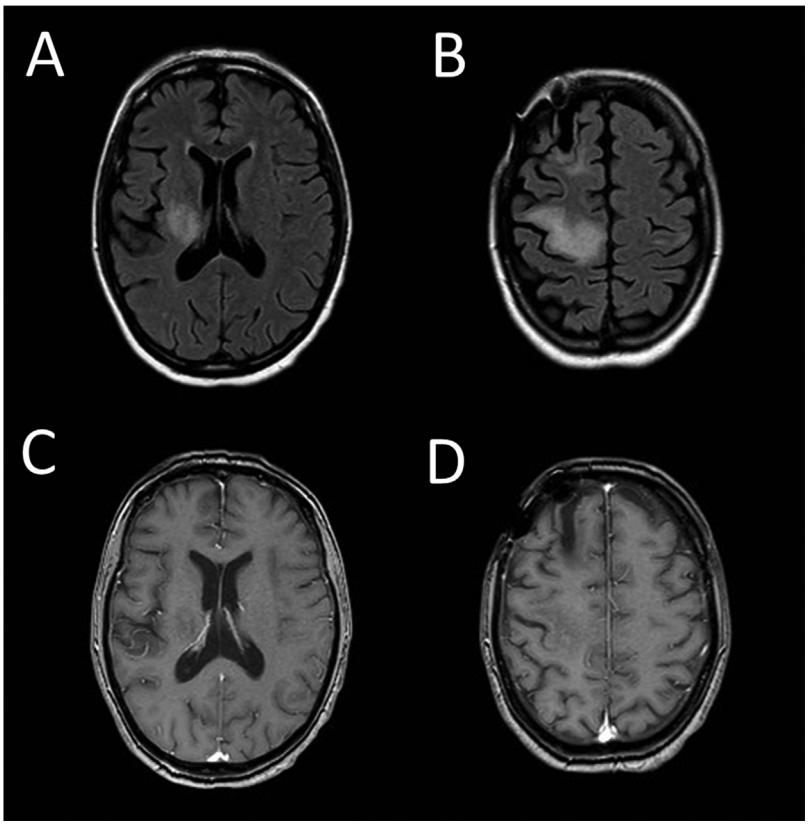

Fig. 6. Axial cuts of brain MRI showing response to treatment with decrease in the extent of the lesion (A, B) and enhancement (C, D) in the bilateral cortical, subcortical lesions. (A: flair right thalamus; B: flair pre-motor cortex; C: gadolinium; D: gadolinium)

In patients with PML, JCV DNA is regularly detected in T and B lymphocytes and in monocytes at low levels. The prevalence of JC viremia increases with age, but viral DNA is rarely present both in blood (2–3%) and other tissues, including the CNS [28]. The few reported cases of PML in the haplo-SCT patients revealed a detectable viral load in the urine as well as detectable DNA and RNA in peripheral blood [29,30]. CSF sampling and MRI of the brain are mandatory for diagnosis of PML. The detection of JCV DNA by CSF PCR has widely replaced the need of brain biopsy for initial diagnosis except in cases where the suspicion for PML remains elevated despite non-diagnostic imaging and CSF analysis. Unfortunately, despite a specificity of 100%, CSF PCR for JCV has a sensitivity of only 50–75% [31,32]. On imaging, the most commonly affected area is the semi-oval center, although the posterior cranial fossa can be involved as well. The diagnostic classification includes "histology- confirmed" PML (positive JCV-DNA by PCR on brain biopsy), "laboratory-confirmed" PML (positive JCV DNA by PCR in CSF), and "possible" PML suggested by typical clinical and radiological findings in the absence of JCV DNA in biological samples [33]. Mateen et al. have reported that 44% of PML cases in the transplant literature have been diagnosed with a brain biopsy whereas 24% were diagnosed with positive PCR for JCV [26].

CNS infections such as HSV, CMV, VZV, HHV-6 and EBV encephalitis as well as drug induced leukoencephalopathy and toxicities must be ruled out. Fungal infections of the CNS, such as cryptococcal meningoencephalitis and *Aspergillus*, must be considered in immunosuppressed patients, but patients are commonly febrile and imaging usually shows multiple hypointense lesions. Post-HCT, B and T-cell immunophenotyping may aid in determining the risk of development of opportunistic infections as well as the efficacy of immunizations. Steurer et al. emphasized that alloreactive T-cell response can remain severely depressed for months following HCT despite count recovery and 'normal' CD4 lymphocyte numbers [34].

No treatment was proven effective for PML in patients without HIV and currently, the available therapeutic options include nucleoside analogs such as cidofovir and cytarabine [35]. Other described regimens include intravenous immunoglobulins, interleukin-2 [36], interferon [37], zidovudine and ganciclovir as single agents or in combination with cytarabine [38,39]. Donor lymphocyte infusion and withholding GVHD prophylaxis may also play a role in the treatment of patients post allo-HCT [6,26].

Atypical antipsychotic agents, especially risperidone, might be an effective treatment and a key contributor in changing the bad prognosis of PML [40]. They inhibit 5-HT2A, a serotonergic receptor that was found to be essential in JCV replication in the astroglial cells [41]. The results of the initial studies are promising but yet in their infancy, requiring more studies and multidisciplinary efforts [40]. Few reports have been observed after myeloablative treatment, but PML has also been described in the reduced intensity conditioning setting [34,36].

In conclusion, PML is a rare complication occurring in immunosuppressed patients undergoing haplo-SCT. The JCV reactivation in two patients receiving cyclophosphamide post haplo-identical T-cell replete transplantation at our institution raised the suspicion of further immune suppression induced by cyclophosphamide in addition to the use of rituximab in the post-transplant setting. Hence, PML should be suspected when patients present with neurological symptoms, and further diagnostic examinations (CSF samplings, MRI) should be performed. If the initial workup is negative in patients with high suspicion for PML, a brain biopsy should be performed. Larger studies with longer follow-up periods of patients post-haplo-SCT are needed to further describe the risk of JCV reactivation, and achieve a better understanding of the disease course in this patient population,

for an early restoration of the immune function which is essential to improve patient survival.

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6. Disclosure of interest

The authors declare that they have no competing interest.

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