Adoptive Allogeneic T-Cell Therapy Improves the Clinical Outcome of JC Virus Granule Cell Neuronopathy

A Case Report

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Abstract

Objectives
JC virus granule cell neuronopathy is a potentially fatal otherwise highly disabling disease without an approved therapeutic option. This case report presents the positive record to T-cell therapy in JC virus granule cell neuronopathy.

Methods
The patient represented with subacute cerebellar symptoms. Diagnosis of JC virus granule cell neuronopathy was made because of infratentorially accentuated brain volume atrophy shown by brain MRI and the detection of JC virus DNA in the CSF.

Results
Six doses of virus-specific T cells were administered. Within 12 months after therapy initiation, the patient showed clear clinical benefit with improvement of symptoms, and JC viral DNA load significantly declined.

Discussion
We present the case report of a positive response to T-cell therapy in JC virus granule cell neuronopathy, leading to an improvement of symptoms.
JC virus can cause an asymptomatic latent or persistent infection in the immunocompetent population. In primary cellular immunodeficiency, due to autoimmune disorders, malignancies, or pharmacologic interventions, JC virus can reactivate and lead to different disease patterns in the brain, most commonly progressive multifocal leukoencephalopathy (PML). PML is a potentially life-threatening opportunistic infection of the brain due to lytic destruction of glial cells, primarily oligodendrocytes. According to current diagnostic criteria of the American Academy of Neurology, PML diagnosis is made by brain biopsy or is based on the triad of appropriate clinical symptoms, typical imaging findings on brain MRI, and the detection of JC viral DNA in the CSF by PCR. In addition to glial cells, JC virus can infect neuronal cells such as granule cells of the cerebellum.

An almost exclusive infection of granular cells coined the disease entity JC virus granule cell neuronopathy (JCV-GCN). The diagnosis of JCV-GCN is based on clinical symptoms in accordance with cerebellar syndrome, direct detection of JC viral DNA, and dominant cerebellar atrophy on MRI with or without additional lesions suggestive of PML. Pathophysiologically, the shift in JC virus tropism from glial to neuronal infection may be due to viral genetic changes. Cases with JCV-GCN reported so far outline a high grade of disability or even fatal course. To date, there is no approved effective therapy for JC viral infections. Allogeneic virus-specific T-cell therapy is a novel, currently experimental, approach to restore the compromised cellular immune reaction of those affected. Because BK virus (BKV; also known as human polyoma–virus 1) is a ubiquitous human polyomavirus and shares a high sequence homology to JC virus, recent research has focused particularly on BKV-specific T-cell therapy approaches for JC virus–associated diseases.

**Case Presentation**

A 47-year-old female patient underwent long-term immunosuppressive therapy with 5 mg of prednisolone per day and 150 mg of azathioprine per day (each >20 years) and rituximab (>13 years) to treat her Sjögren syndrome. First, neurologic symptoms of severe headache occurred approximately 9 months before presentation to our clinic. Within the previous 6 months, she had developed a progressive gait disorder, visual fixation impairment during head movements, and dysarthria. Intensity of symptoms had increased within the preceding 3 months. Four weeks before admission, another cycle of rituximab therapy with a total of 2 g had been externally administered. Neurologic examination on admission revealed a cerebellar syndrome with dysarthria, dysphagia, saccadic eye movement disorder, ataxia of all limbs, and tendon hyperreflexia at all sides. Within the short-term inpatient course, the clinical condition deteriorated rapidly with new onset of complete bilateral facial palsy, anarthria, dysphagia severe enough to warrant placement of a percutaneous endoscopic gastrostomy, and progressive visual loss to almost complete blindness. Furthermore, there was fluctuating eye muscle paresis. Consecutively, the patient became bedridden.

An examination of the brain MRI showed severe cerebellar atrophy (Figure 1) with evidence of T2 signal hyperintensities pontine and in the crurae cerebri (Figure 2). Fluorodeoxyglucose-PET/CT (FDG-PET/CT) revealed cerebellar glucose hypometabolism. In addition to mild blood-CSF barrier dysfunction (CSF/serum albumin quotient 9.29; standard age adjusted <7.13), CSF analysis revealed positive JC virus DNA of 2,000 copies/mL, detected by PCR. Further results of a comprehensive laboratory examination revealed lymphopenia (700/μL), a mild antibody deficiency syndrome (IgM 0.39 g/L, standard 0.4–2.3 g/L; IgA 0.64 g/L, standard 0.7–4.0 g/L; IgG 7.58 g/L, standard 7.0–16.0 g/L), a monoclonal gammopathy of the IgG kappa type, and positive anti-SSA(Ro) antibodies consistent with Sjögren syndrome. Other differential diagnostic laboratory analyses remained without abnormalities (Table 1). The diagnosis of JCV-GCN was made. Immunosuppressive therapy with azathioprine was discontinued. An experimental therapy with pembrolizumab was not possible due to the preexisting autoimmune disease, which displays a contraindication. Because an approved therapy for JCV-GCN is not available, we decided to use the new

![Figure 1 Severe Cerebellar Atrophy During Diagnosis Detected by Brain MRI (A Sagittal Plane, B Transversal Plane)](image-url)
experimental therapy with administration of allogeneic, partially human leukocyte antigen-matched BKV-specific T cells. In total, the patient received 6 doses of BKV-specific T cells intravenously, divided into 2 cycles of 3 applications each, consisting of 1 fresh product followed by 2 doses of cryopreserved products. Each product contained 20,000 CD3-positive T cells per kilogram body weight. The therapy was tolerated without any side effects.

During the course of the therapy, the patient showed clear clinical benefits: 12 months after initial presentation, she was able to stand and walk independently. She regained the possibility of oral food intake and is no longer dependent on percutaneous tube feeding. Her dysarthria improved, enabling her to communicate verbally, and her visual acuity increased. An examination of the brain MRI revealed a reduction of T2 hyperintensity within the brainstem, and JC viral DNA load significantly declined (<500 copies/mL). During the course, sequence analysis of the viral genome was performed. The noncoding control region (NCCR), an important regulatory region that harbors the origin of viral DNA replication, strongly resembled the organization of the archetype: a nucleotide substitution in block C (position 107) and D (position 159) and a deletion of 2 nucleotides (guanine-guanine) between blocks E and F, leading to the conversion from thymine to proline. Within the last current follow-up 20 months after therapy initiation (12 months after last T-cell admission), the patient remained clinically stable at an improved level.

**Discussion**

We present the case report of a positive response to allogeneic BKV-specific T-cell therapy in JCV-GCN, leading to an improvement of symptoms and long-term survival. Furthermore, the NCCR with persistently reduced JC viral DNA load could be identified as an archetypal subtype, likely representing a less.
pathogenic virus isolate after successful resolution of the disease, as already observed in patients with PML.1

Adoptive transfer of virus-specific T cells is a promising therapeutic approach for treating severe opportunistic viral infections without major side effects. We have gained experience in treating PML with BKV-specific T cells over the past 2 years and have published the first 2 cases.12 Since 2018, different case series and an open-label, single-cohort pilot study support the positive therapeutic effect of adoptive allogeneic BKV-specific T-cell transfer in PML.12-14

After the therapeutic approach of PML treatment, our patient with JCV-GCN was successfully treated with adoptively transferred allogeneic partially human leukocyte antigen-matched BKV-specific T cells. JCV-GCN represents a rare disease, and depending on the immunosuppressive constitution, different outcome scenarios have been described so far, ranging from severe disabling to reaching a stable state after reconstitution of the immune system and death.5,8 Our patient has improved from being bedridden, bulbar symptoms with anarthria, and need for external feeding to independence in her own home with residual symptoms. It is possible that the discontinuation of azathioprine had a partial impact on the further positive course. However, due to the rapid deterioration and the very poor clinical condition, we do not assume that the patient would have recovered without the therapy with BKV-specific T cells.

Supplementary to our case, in 2021, a case report of a patient experiencing JCV-GCN who was treated with BKV-specific cytotoxic T-lymphocyte lines generated ex vivo and showing a partial response was reported.15 The patient experienced frequent urinary tract infections and influenza A with progressive weakness and was transferred to a hospice care in the course of time.15

In conclusion, in addition to differential diagnoses such as paraneoplastic syndromes, malignant cerebellar processes, and common infectious or metabolic/pharmacologic causes, an opportunistic viral infection in the sense of a JCV-GCN should be considered when immunocompromised patients present with subacute cerebellar syndrome. Adoptive transfer of allogeneic BKV-specific T cells represents an innovative experimental therapeutic approach for this disease.

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## Appendix

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## References


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