Meningoencephalitis Associated with Archetype-like JC Polyomavirus and Complete Neurological Recovery

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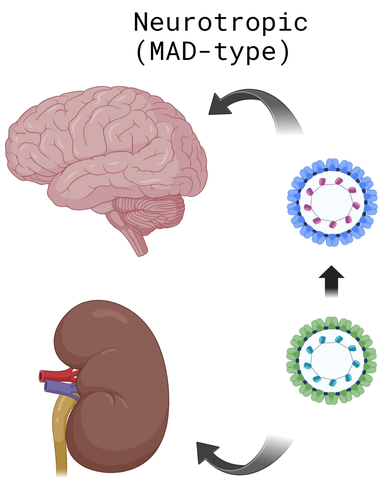
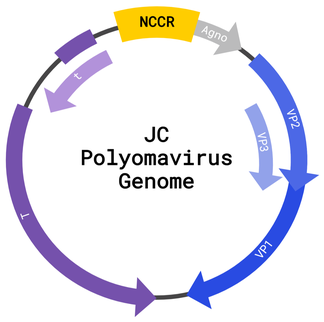
Introduction

JC Polyomavirus (JCPyV) infects 40-60% of the population. Generally, it is asymptomatic and takes residence in the kidney with occasional shedding in the urine. In immunocompromised patients it can travel to the brain causing a debilitating and often lethal infection known as Progressive Multifocal Leukoencephalopathy (PML). There is no known cure for JCPyV and patients who survive the infection are left with severe neurological deficits[1].



Progression to neurologic disease is thought to be associated with rearrangement of the noncoding region of the genome known as the NCCR region. Cases of PML and Granule Cell Neuronopathy (GCN) generally contain several insertions and deletions in this region while virus in the kidney known as archetype does not contain these changes2,3. In this case we present a novel patient who presented with JCPyV associated encephalopathy possessing an archetype-like NCCR who achieved full recovery of symptoms after six months.



Case

A 61-year-old female lung transplant patient presented with acute neurological symptoms eleven months post transplant. She had been adhering closely to her anti-rejection regimen. Symptoms included confusion, slurred speech, right facial droop, and right hand paresthesia. CSF qPCR was positive for JCV (Figure 1), but brain MRI showed no FLAIR lesions diagnostic for PML (Figure 2). Her anti-rejection regimen was reduced and JCV copy numbers in her CSF decreased. Four months after initial presentation she was near neurological baseline and plasma and CSF JCV were trending downwards (Figure 1).

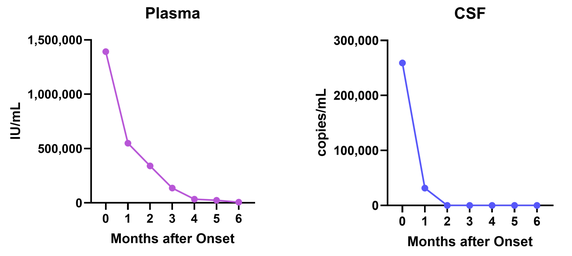


Figure 1 Quantification of virus in clinical isolates of plasma and CSF in the first six months after disease presentation.

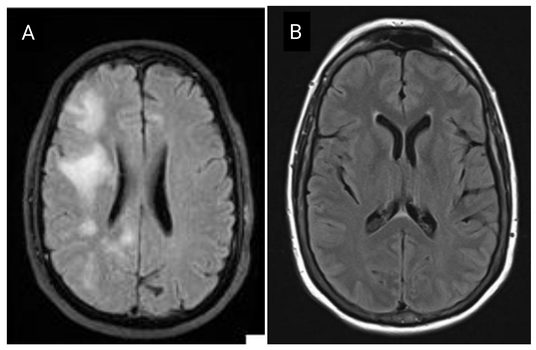


Figure 2 MRI of a classic PML patient[4] (A) and our case study (B). Multiple lesions with demyelination are seen in the classic PML patient, while the case study patient has no apparent lesions.

Genomic Analysis

PCR was used to amplify the virus from the clinical samples of CSF, plasma, and urine. The urine had insufficient viral titers to produce PCR product, but full length genomes from CSF and plasma were amplified. The genomes were then sequenced and compared to existing sequences for archetype and neurotropic JC viruses. The sequence of plasma and CSF from the case patient were found to be identical. Interestingly the NCCR region of the patient more closely matched that of Archetype than that of MAD-type or other neurotropic strains (Figure 3). A few single base pair substitutions were the only differences from archetype. Along the rest of the genome the virus better matched MAD-1 in its base-pair substitutions, but the changes resulted in very few amino acid changes. When blasted against Genbank the sequence most closely matched a strain isolated from a case of JC nephropathy with no neurological complications[5].

Conclusions

This is a unique case of JC encephalopathy where the patient achieved remarkable clinical recovery after a few months with reduced immune suppression. Additionally, it is novel to find a case of neurotropic JCPyV with an archetype NCCR that is similar to a published strain causing nephropathy. This changes what we thought we knew about the tropism of JC virus in the brain and its clinical prognosis.

Future Directions

- Develop infection model for primary kidney and oligodendrocyte cells.
- Outgrow virus in primary cells and sequence virus adaptation to cell type over time.
- Develop kidney and neural organoid models to identify specific cells infected by strains of JCPyV.
- Use humanized mouse model to map path JC virus takes from kidney to the brain.
- Compare various JC strains from clinical time courses to map JC adaptations in vivo.

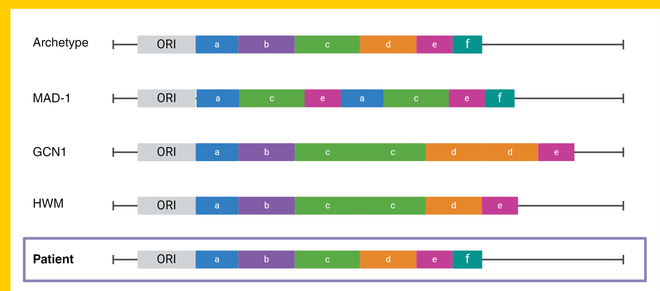


Figure 3 Comparison of the NCCR regions of several known JC virus strains. Segments are divided into six segments A-F as precedent in literature. MAD-1 is a known PML strain [6], Granule Cell Neuronopathy (GCN) and Hemispheric White Matter (HWM)[3] are other unique presentations of neurotropic JCPyV.

References

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