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Progressive Multifocal Leukoencephalopathy in a Renal Transplant Recipient with Newly Diagnosed Human Immunodeficiency Virus and Chronic Myeloid Leukemia

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Case Report

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare, often fatal demyelinating disease caused by reactivation of JC virus (JCV) in immunocompromised hosts. Post-transplant PML is uncommon but carries high mortality and limited treatment options. We describe a 49-year-old man with two prior renal transplants, prolonged multi-agent immunosuppression, repeated rituximab exposure, newly diagnosed HIV infection, and chronic myeloid leukemia who developed seizures, aphasia, and tremor three years after his second transplant. MRI revealed multifocal white matter lesions involving the parietal, occipital, brainstem, and cerebellar peduncle regions; cerebrospinal fluid studies were unremarkable, and brain biopsy confirmed simian virus 40 (SV40) positive PML. Despite reduction of immunosuppression, the patient died three months after diagnosis. This case highlights the convergence of multiple recognized PML risk factors — solid-organ transplantation, cumulative rituximab exposure, and newly diagnosed HIV — in a single patient, and illustrates seizures as an atypical but important presenting feature arising from cortically adjacent demyelinating lesions. Clinicians should maintain a high index of suspicion for PML in immunocompromised patients with new neurologic symptoms, as diagnosis often requires brain biopsy when cerebrospinal fluid PCR is negative or unavailable. Given the absence of curative antiviral therapy, management remains centered on immune reconstitution, balanced against the risk of graft rejection in transplant recipients. As the use of biologic and immunosuppressive agents expands, clinicians should anticipate rising PML incidence and the ongoing need for targeted, blood-brain-barrier-penetrant antiviral therapies.

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease caused by reactivation of the John Cunningham virus (JCV) in immunocompromised hosts, leading to destruction of oligodendrocytes (Brooks and Walker 1984). It occurs in patients with HIV infection, hematologic malignancy, solid-organ transplantation, or exposure to monoclonal antibody therapies such as natalizumab and rituximab (Brooks and Walker 1984). Post-transplant PML is rare, with an incidence of 0.027% among renal transplant recipients, but is frequently rapidly progressive and fatal, with limited treatment options (Eng et al. 2006). We report a 49-year-old man with two prior renal transplants, prolonged immunosuppression, rituximab exposure, newly diagnosed HIV, and chronic myeloid leukemia (CML) who presented with seizures and imaging findings ultimately confirmed as PML by brain biopsy.

Case Summary

A 49-year-old man with hypertension-induced renal dysfunction progressed to end-stage renal disease over eight years, requiring hemodialysis. In 2013, he underwent his first living-donor renal transplant, maintained on tacrolimus, mycophenolate mofetil, and steroids; the graft was lost to rejection three years later despite anti-thymocyte globulin (ATG) and steroids.

In 2018, he received a second living-donor transplant. Pre-transplant single-antigen bead testing was positive for donor-specific antibodies, requiring desensitization with two doses of rituximab, plasmapheresis, and intravenous immunoglobulin; ATG induction and standard triple immunosuppression followed. One month post-transplant he developed biopsy-proven antibody-mediated rejection, treated with rituximab and plasmapheresis, with later recurrence managed by intravenous steroids; creatinine stabilized between 1.8 and 2.1 mg/dL.

Three years after the second transplant, he presented with leukocytosis and anemia; bone marrow biopsy confirmed BCR-ABL–positive CML, and dasatinib was started. Workup incidentally revealed HIV infection (CD4 282/mm³, viral load 1,720,000 copies/mL), and antiretroviral therapy with dolutegravir/emtricitabine/tenofovir alafenamide was initiated.

Two months later, he developed seizures, aphasia, and bilateral hand tremors. MRI showed gliosis in the left parietal and right occipital lobes with multifocal juxtacortical and deep white matter lesions bilaterally, middle cerebellar peduncle involvement as well as the brainstem. Cerebrospinal fluid analysis was negative for tuberculosis and malignant cells, and CSF JCV PCR was negative, prompting brain biopsy. Biopsy of the left parietal lesion showed non-neoplastic tissue with lymphocytic cuffing and SV40 positivity, confirming PML. Despite reduction of immunosuppression, he deteriorated and died three months after diagnosis.

Discussion

PML results from reactivation of JC virus (JCV), a ubiquitous polyomavirus to which 50–90% of adults are seropositive, but clinical disease remains rare (prevalence 4.4 per 100,000) and typically requires significant immunosuppression from HIV/AIDS, hematologic malignancy, or transplantation (Tan and Koralnik 2010; Brew et al. 2010). Post-transplant PML occurs in an estimated 0.027% of renal transplant recipients; recognized risk factors include pre-transplant blood transfusion, elevated panel reactive antibody, and immunosuppressive agents such as mycophenolate mofetil (Hildreth and Alcendor 2021; Neff et al. 2008), while monoclonal antibody therapies including rituximab and natalizumab are also linked to rising incidence (Eng et al. 2006).

Prognosis is poor in the absence of specific antiviral therapy: three-month untreated mortality ranges from 20–50%, with death typically within six months of diagnosis (Brew et al. 2010; Crowder et al. 2005). JCV persists quiescently in kidney, bone marrow, and lymphoid tissue after primary infection, and reactivation is associated with rearrangements of the viral regulatory region (Tan and Koralnik 2010; Jensen and Major 2001).

Clinical presentation is heterogeneous, most commonly motor weakness, speech disturbance, and cognitive impairment (Crowder et al. 2005). Seizures occur in approximately 20% of cases and, though PML is classically a white matter disease, are attributed to demyelinating lesions adjacent to cortical grey matter, as in our patient (Tan and Koralnik 2010). MRI is the diagnostic modality of choice, typically showing T2/FLAIR-hyperintense, T1-hypointense lesions (Brew et al. 2010). Definitive diagnosis requires

JCV DNA detection in cerebrospinal fluid by PCR; when PCR is negative despite strong clinical suspicion, as in our patient, stereotactic brain biopsy remains the gold standard (Brew et al. 2010; Anand et al. 2019).

Treatment centers on immune reconstitution. In HIV-positive patients, combination antiretroviral therapy yields one-year survival of 39–56%, correlating with baseline CD4 count (De Luca et al. 1998; Marzocchetti et al. 2009a). In HIV-negative patients, reducing immunosuppression is the primary strategy despite the risk of graft rejection; median survival among transplant recipients is approximately 6.4 months, with 84% mortality (Hildreth and Alcendor 2021). Investigational approaches — JCV-specific dendritic cell vaccines, plasma exchange to accelerate natalizumab clearance, and in vitro-active agents such as mirtazapine, mefloquine, and cidofovir — have shown limited clinical benefit to date (Marzocchetti et al. 2009b; Brickelmaier et al. 2009; Elphick et al. 2004).

This case highlights the rarity of post-transplant PML and illustrates how cumulative immunosuppressive exposures may synergistically increase susceptibility to JCV reactivation. Beyond long-term post-transplant immunosuppression, our patient had repeated rituximab exposure, newly diagnosed HIV infection, and CML — multiple recognized PML risk factors converging in a single individual. Seizures as the presenting manifestation, together with the need for brain biopsy despite nondiagnostic cerebrospinal fluid studies, further emphasize the diagnostic challenges this condition poses.

Conclusion

Patients with HIV, hematologic malignancy, transplantation, or biologic therapy exposure require vigilant monitoring for neurologic symptoms of PML, including seizures, an atypical but recognized presentation. Management of transplant recipients is particularly challenging, requiring a balance between immune reconstitution to combat JCV and preservation of graft function. No curative therapy currently exists, and mortality remains high. As biologic and immunosuppressive therapy use expands, PML incidence is expected to rise, underscoring the need for targeted antiviral agents capable of crossing the blood-brain barrier (Hildreth and Alcendor 2021).

Declarations

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Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval / Informed Consent

Written informed consent for publication of this case, including clinical details, was obtained from the patient's next of kin.

References

1. Anand P, Hotan GC, Vogel A, Venna N, Mateen FJ (2019) Progressive multifocal leukoencephalopathy: a 25-year retrospective cohort study. Neurol Neuroimmunol Neuroinflamm 6:e618. 10.1212/NXI.0000000000000618
2. Brew BJ, Davies NW, Cinque P, Clifford DB, Nath A (2010) Progressive multifocal leukoencephalopathy and other forms of JC virus disease. Nat Rev Neurol 6(12):667–679. 10.1038/nrneurol.2010.164
3. Brickelmaier M, Lugovskoy A, Kartikeyan R, Reviriego-Mendoza MM, Allaire N, Simon K, Frisque RJ, Gorelik L (2009) Identification and characterization of mefloquine efficacy against JC virus in vitro. Antimicrob Agents Chemother 53(5):1840–1849. 10.1128/AAC.01614-08
4. Brooks BR, Walker DL (1984) Progressive multifocal leukoencephalopathy. Neurol Clin 2:299–313
5. Cinque P, Koralnik IJ, Clifford DB (2003) The evolving face of human immunodeficiency virus-related progressive multifocal leukoencephalopathy: defining a consensus terminology. J Neurovirol 9(Suppl 1):88–92
6. Crowder CD, Gyure KA, Drachenberg CB, Werner J, Morales RE, Hirsch HH, Ramos E (2005) Successful outcome of progressive multifocal leukoencephalopathy in a renal transplant patient. Am J Transpl 5(5):1151–1158. 10.1111/j.1600-6143.2005.00800.x
7. De Luca A, Ammassari A, Cingolani A, Giancola ML, Antinori A (1998) Disease progression and poor survival of AIDS-associated progressive multifocal leukoencephalopathy despite highly active antiretroviral therapy. AIDS 12:1937–1938
8. Elphick GF, Querbes W, Jordan JA, Gee GV, Eash S, Manley K, Dugan A, Stanifer M, Bhatnagar A, Kroeze WK, Roth BL, Atwood WJ (2004) The human polyomavirus, JCV, uses serotonin receptors to infect cells. Science 306(5700):1380–1383. 10.1126/science.1103492
9. Eng PM, Turnbull BR, Cook SF, Davidson JE, Kurth T, Seeger JD (2006) Characteristics and antecedents of progressive multifocal leukoencephalopathy in an insured population. Neurology 67:884–886
10. Hildreth JEK, Alcendor DJ (2021) JC Polyomavirus and Transplantation: Implications for Virus Reactivation after Immunosuppression in Transplant Patients and the Occurrence of PML Disease. Transplantology 2(1):37–48. 10.3390/transplantology2010004
11. Jensen PN, Major EO (2001) A classification scheme for human polyomavirus JCV variants based on the nucleotide sequence of the noncoding regulatory region. J Neurovirol 7:280–287

12. Marzocchetti A, Tompkins T, Clifford DB, Gandhi RT, Kesari S, Berger JR, Simpson DM, Prosperi M, De Luca A, Koralnik IJ (2009a) Determinants of survival in progressive multifocal leukoencephalopathy. Neurology 73(19):1551–1558. 10.1212/WNL.0b013e3181c0d4a1
13. Marzocchetti A, Lima M, Tompkins T, Kavanagh DG, Gandhi RT, O'Neill DW, Bhardwaj N, Koralnik IJ (2009b) Efficient in vitro expansion of JC virus-specific CD8 T-cell responses by JCV peptide-stimulated dendritic cells from patients with progressive multifocal leukoencephalopathy. Virology 383(2):173–177. 10.1016/j.virol.2008.10.046
14. Neff RT, Hurst FP, Falta EM, Bohen EM, Lentine KL, Dharnidharka VR, Agodoa LY, Jindal RM, Yuan CM, Abbott KC (2008) Progressive multifocal leukoencephalopathy and use of mycophenolate mofetil after kidney transplantation. Transplantation 86(10):1474–1478. 10.1097/TP.0b013e31818b62c8
15. Tan CS, Koralnik IJ (2010) Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 9(4):425–437. 10.1016/S1474-4422(10)70040-5