

Shivali Patel MD<sup>1</sup> and Kinza Tareen MD<sup>2</sup>

<sup>1</sup>Department of Psychiatry, Henry Ford Health; <sup>2</sup>Department of Psychiatry, Michigan Medicine


**INTRODUCTION**

- The differential for neuropsychiatric symptoms following solid organ transplantation is broad, including infection, posterior reversible encephalopathy (PRES), and substance use
- Post-transplant lymphoproliferative disorder (PTLD) is a rare complication of transplantation, affecting an estimated 2-20% solid organ and hematopoietic transplant recipients (**1,2**)
- Various factors are associated with increased risk, including Epstein-Barr Virus (EBV) seropositivity in donor and negativity in recipient and high dose immunosuppression
- Management starts with reduction of immunosuppression
- Rituximab, a monoclonal anti-CD20 antibody, is a mainstay treatment of EBV+ PTLD refractory to immunosuppression reduction
- The utility of rituximab in the treatment of psychotic disorders is being investigated (**3**), but rituximab has infrequently been associated with psychiatric side effects (**4**)
  - Per package insert, depression and anxiety are possible psychiatric side effects, especially in patients predisposed to psychiatric symptoms (**1,5**)
- Here, we present a rare case of a liver transplant (LT) recipient who was diagnosed with PTLD and later developed psychotic symptoms following the initiation of rituximab therapy

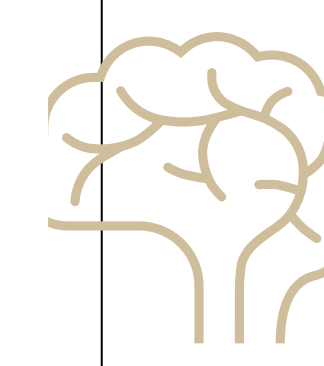
**CASE PRESENTATION**

- A 34-year-old male with a history significant for ulcerative colitis, and primary sclerosing cholangitis (PSC) on adalimumab underwent 2 LTs secondary to recurrent PSC
- He was diagnosed with PTLD 3 years after his second LT after initially presenting with fatigue, fever, and pancytopenia
  - EBV donor positive, recipient negative
  - Magnetic resonance imaging demonstrated enlarged retroperitoneal lymph nodes
  - Retroperitoneal lymph node biopsy demonstrated polymorphic PTLD with Hodgkin-like cells present
  - Excisional axillary lymph node biopsy demonstrated polymorphic PTLD
  - To minimize immunosuppression, adalimumab was discontinued, and doses of tacrolimus and prednisone were reduced
- He received 4 weekly doses of rituximab 600 mg/m<sup>2</sup> for PTLD and was admitted for encephalopathy two weeks following fourth dose
  - Collateral suggested that he developed new visual hallucinations and confusion days after his recent rituximab infusion and was found unresponsive ten days later, prompting hospitalization
  - No other known precipitating or perpetuating factors
  - Patient had no known genetic loading for psychotic or bipolar disorders
- Extensive work-up, including brain magnetic resonance imaging, flow cytometry, electroencephalogram, urine toxicology, metabolic, infectious, and autoimmune and paraneoplastic serum and cerebrospinal fluid studies, was unrevealing
- He was maintained on tacrolimus and low dose prednisone as there was low clinical suspicion PRES and delirium
- Transplant psychiatry was consulted on day 7 of hospitalization due to concerns for catatonia
- Initial evaluation revealed a Bush Francis Catatonia Rating Score of 10 notable for mutism, staring, waxy flexibility, and autonomic instability
- Catatonic symptoms lysed with lorazepam (up to 8 mg/day)
- However, paranoid and nihilistic delusions, audiovisual hallucinations, and gross disorganization with marked irritability soon became apparent, culminating in psychiatric hospitalization
- During inpatient psychiatric admission, benzodiazepines were tapered off and his psychotic symptoms improved significantly with olanzapine 10 mg and valproate 500 mg.
- Transplant psychiatry follow-up one month after discharge revealed no decompensated psychiatric symptoms
- Fluorodeoxyglucose-positron emission tomography scan and flow cytometry two months following rituximab treatment suggested complete resolution of PTLD
- As EBV titer decreased over 20-fold, rituximab maintenance treatment was considered
- He was ultimately advised to taper off valproate while continuing olanzapine until further assessment

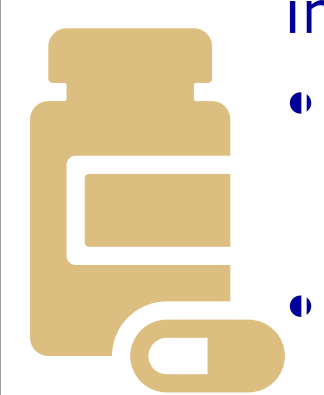
**PTLD AND RITUXIMAB IN THE LITERATURE**



Diagnosis of PTLD requires a high index of suspicion and should be considered in a patient who has undergone allogeneic transplantation and presents with adenopathy, B symptoms, and unexplained hematologic or biochemical abnormalities




PTLD may have direct central nervous system (CNS) involvement and subsequently present with mental status changes and new neurological findings (**11,12**)



Risk of PTLD may vary depending on type of immunosuppressant medication (**13**)

- Higher risk with tacrolimus, azathioprine, belatacept, antithymocyte globulin, and OKT3
- No increased risk with mycophenolate mofetil, basiliximab, daclizumab
- Variable risk with cyclosporine, mTOR inhibitors, and alemtuzumab



PTLD is a risk factor for graft loss and may present with similar symptoms of organ rejection or symptoms of other immunosuppressive medications

**Select cases of rituximab-associated neuropsychiatric symptoms**

Case Description	Proposed mechanism
A patient with non-paraneoplastic limbic encephalitis received intravenous immunoglobulin therapy and plasmapheresis developed a brief manic episode following treatment with rituximab ( <b>6</b> )	Rituximab may be associated with an aberrant immune response in patients with underlying autoimmune disorders
A recipient of a heart ( <b>7</b> ) and a kidney ( <b>8</b> ) transplant developed PRES following rituximab initiation, presenting with visual disturbances including photophobia and hallucinations	Rituximab may cross the blood brain barrier more easily in immunocompromised patients, resulting in cell-mediated autoimmune reactions with possible capillary leakage syndromes, ultimately leading to endothelial damage and dysfunction
Patients treated with rituximab may develop progressive multifocal leukoencephalopathy (PML) which may present with changes in cognition, language, speech, vision, coordination, balance, sensation, and strength and rapidly progress to dementia, blindness, paralysis, coma, and death ( <b>9</b> )	Rituximab involves prolonged B-lymphocyte depletion which in turn impairs the ability of the immune system to control latent John Cunningham virus
A patient with non-Hodgkin lymphoma demonstrated temporary manic symptoms following first, second, and third doses of rituximab ( <b>10</b> )	Rituximab may promote cytokine release, and these effects may be compounded by other immunoregulatory medications

**DISCUSSION**

- Given the absence of prodrome and temporal relationship, we suspect our case represents the first known manifestation of catatonia and psychosis following rituximab treatment for PTLD
  - Based on neuroimaging, less likely the patient’s psychiatric disturbances were secondary to PRES or PML
  - PSC may increase risk of PTLD in LT recipients (**14**), so it is possible that the patient’s overall neuropsychiatric symptoms were a manifestation of an inflammatory and neuronal stress diathesis
- CNS PTLD in transplant recipients may present with mental status changes and new neurologic findings, but a review of the literature suggests there is an overall limited understanding of the neuropsychiatric effects of PTLD and rituximab
- Limitations
  - EBV (**15**), tacrolimus (**16, 17**), and prednisone (**18**) have been associated with psychiatric symptoms
    - The patient had a high EBV titer and was maintained on tacrolimus and prednisone, so it is possible these factors may have contributed to the psychiatric disturbances, but less likely any one of these were the primary cause given the absence of neuropsychiatric signs/symptoms prior to rituximab initiation
  - Presentation may have been influenced by untreated premorbid depressive symptoms, though history suggested depressive symptoms were mild in severity
  - Patient has only been followed for a limited duration at the Transplant Psychiatry clinic
    - Unclear if psychotic symptoms or catatonia will re-emerge in the setting of possible rituximab maintenance
    - Unclear if there is a dose-dependent relationship between rituximab and neuropsychiatric symptoms
- Further characterization of PTLD and rituximab-associated psychiatric disturbances is necessary for early identification and management, mitigating the risk of post-transplant complications, and optimizing support for patients, families, and transplant teams.

