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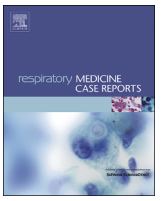

Case Report

A case report of a lung transplant recipient receiving belatacept in combination with low dose tacrolimus complicated by progressive multifocal leukoencephalopathy

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ABSTRACT

Belatacept is a novel T-cell costimulation blockade agent that has unresolved controversy in lung transplant recipients. Belatacept has been recognized as a calcineurin sparing agent for solid organ transplant recipients after reported success in renal transplant patients, despite limited evidence in other transplant recipients. We present the first case of a lung transplant recipient receiving Belatacept, in combination with low dose calcineurin inhibitor, who developed progressive multifocal leukoencephalopathy. While Belatacept without calcineurin inhibitor has been associated with increased risk of acute rejection in solid organ transplant recipients, its infectious risk profile in combination with calcineurin inhibitor remains unclear.

1. Introduction

Belatacept is a novel T-cell costimulation blockade agent approved in renal transplantation. In recent years there has been an increase in use of Belatacept as a calcineurin inhibitor (CNI)- sparing immunosuppression regimen in lung transplantation, however, the efficacy and complications of this regimen is not well delineated. Reports suggest increased incidence of infections with Belatacept [1–4]. We present the case of progressive multifocal leukoencephalopathy (PML) associated with Belatacept use in a lung transplant recipient.

2. Case report

A 67-year-old male with a history of emphysema underwent single right lung transplantation in 2015. His post-transplant course was complicated by tacrolimus related chronic kidney disease (CKD). His immunosuppression was subsequently modified four years after transplant to combination of Belatacept plus low dose tacrolimus (trough 4–6 ng/dl), mycophenolic acid, and prednisone. He had mild improvement of his CKD while on this regimen. Two years later, at the age of 73, he presented with six months of progressive left sided hemiparesis, pseudobulbar symptoms, and mild cognitive deficits. Initial CT head stroke protocol was negative for cerebral vascular accident. Subsequent brain MRI revealed bilateral parietal white matter enhancement, right greater than left (Fig. 1).

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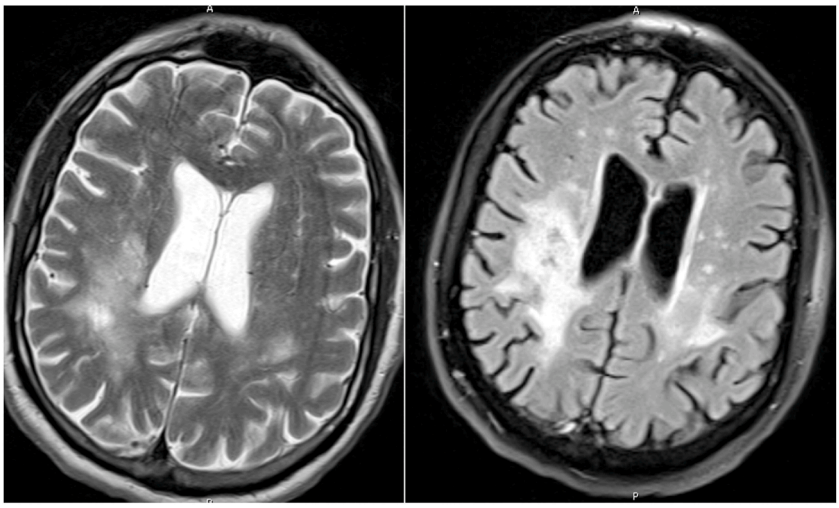

Fig. 1. Initial Brain MRI In Our Patient Supporting Diagnosis of PML T2 Flair
There is bilateral asymmetric right greater than left parietal predominant confluent T2/FLAIR signal abnormality in the subcortical, deep, and periventricular white matter compartments. There is additional involvement of the corpus callosum splenium and right posterior limb internal capsule.

Extensive serum and cerebrospinal fluid analysis were negative for usual infectious etiology or malignancy however tested positive for JC Virus. After the diagnosis of PML was made, Belatacept and mycophenolic acid were stopped. A treatment regimen with mefloquine and mirtazapine was also implemented. Over the next several months he experienced a progressive decline despite aggressive neurorehabilitation. Repeat MRI three months after discharged showed no improvement in known lesions. In addition, he developed a PET positive lung nodule concerning for malignancy but further work up was declined. The patient passed away in June 2023, approximately a year after his diagnosis.

3. Discussion

Belatacept is a human fusion protein combining the constant-region fragment (Fc) of human IgG1 and the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) [4]. It is a selective costimulation blocker that binds to costimulatory ligands CD80 and CD86 of the B7 family on antigen presenting cells (APCs). These costimulatory ligands are responsible for the full activation of naive T-cells when bound to their CD28 receptor. T cell apoptosis and anergy result from blockade of the APC costimulatory ligands and respective T cell receptors.

Monthly intravenous infusion of Belatacept was FDA-approved for use in kidney transplant recipients, after two multicentered randomized control trials demonstrated noninferiority between Belatacept based regimens against Cyclosporine in renal transplant patients [5,6]. However, it was later associated with higher rates of rejection when used alone after 6 months and combination with a lower dose CNI improved this morbidity [7]. Despite its success in renal transplantation, its place in immunosuppression for lung transplantation remains unclear. A summary of studies that have investigated Belatacept in lung transplantation is provided in Table 1.

In a case series of eleven lung transplant recipients, Belatacept demonstrated no difference in acute or chronic rejection, infection, hemodynamic changes, or death when used to replace calcineurin inhibitor [3]. Patients who received Belatacept-based regimen showed improvement in renal function, consistent with studies on renal transplant recipients. Nevertheless, using Belatacept without CNI has been associated with an increased incidence of acute cellular rejection. Several studies have reported severe rejection associated with CNI free Belatacept use [8,9]. This observation has been attributed to the lack of inhibition of a key T cell activation pathway by Belatacept compared to CNI based immunosuppression. Although naïve T cells require costimulatory signal via CD28 for full activation following an antigenic stimulus, the absence of CD28 in effector memory and CD8 positive tissue-resident memory T-cells make them resistant to the effect of Belatacept [14,15]. As a result, many experts suggest its use in combination with low CNI trough targets, despite uncertainty of optimal trough targets. Belatacept requires no therapeutic monitoring, and no dose adjustment is necessary in renal dysfunction, liver dysfunction, and geriatric age groups.

From an infectious standpoint, Belatacept has been associated with an increased risk of developing viral, bacterial, and fungal infections [1–4,10]. There is limited evidence suggesting increased risk of EBV-positive post-transplant lymphoproliferative disorder (PTLD) when Belatacept is used in comparison to CNI [5,6]. In a recent randomized controlled trial of de novo Belatacept based immunosuppression in lung transplantation, the trial was terminated due to a higher mortality rate in the Belatacept group compared to the control. The authors reported a viral etiology for death in three out of five death in the Belatacept arm [11]. Interestingly, in this trial, there was no overall difference in the incidence of infection and rejection between cohorts, underlining the possibility of worse outcomes from viral infections with the use of Belatacept. The increased risk of infection in patients receiving Belatacept is likely explained by CD28 mediated costimulatory signal blockade, resulting in anergy and apoptosis of naïve T cells, and impaired memory T cell formation, which demonstrate reduced proliferation, migration, and survival [12].

Table 1
Reported De novo Infectious Complications of Belatacept in Lung Transplant Recipients.

Author	Type of Study	Patients experience infection/Total number of patients	Belatacept or Belatacept + low dose CNI	Associated infection
Brugiere et al. [9]	Case series	3/10	Both	Varicella Zoster Virus Pneumocystosis[a]
Iasella et al. [3]	Case series	4/11	Both	Aspergillosis Pseudomonas Stenotrophomonas Adenovirus
Bellinger et al. [1]	Prospective Cohort	41/85	Belatacept + low dose CNI	Aspergillosis CMV NTM
Timofte et al. [4]	Case series	4/8	Belatacept + low dose CNI	Klebsiella *Enterobacter cloacae* Pseudomonas Influenza
Haidar et al. [2]	Case report	1/1	Belatacept	Aspergillosis Adenovirus
Huang et al. [11],[b]	Randomized Control Trial	11/13	Belatacept + low dose CNI[c]	CMV Respiratory viruses including Covid-19 Bacterial Pneumonia Fungal Pneumonia

[a] Report may have been related to prophylaxis non-adherence.
[b] Did not provide specific names of infections.
[c] In the Belatacept arm, CNI was stopped on day 30 and followed until day 365.

Here we report a case of PML, a fatal neurodegenerative disease caused by JC virus, in a lung transplant patient after initiation of Belatacept based immunosuppression. In a review of literature, there are only a few cases of PML in kidney and liver transplant patients using Belatacept based immunosuppression [13,14]. To the best of our knowledge, this is the first case report in a patient with thoracic organ transplantation who developed PML after conversion of immunosuppression to Belatacept based regimen.

It worth mentioning while the increased risk of infection using Belatacept is explained as a result of costimulatory signal blockade and T cell anergy, the increased risk of rejection (when used without CNI) with Belatacept in solid organ transplant patients is intriguing. This paradox of increased of rejection is likely due to the lack of CD28 expression in effector memory T cells that do not require costimulation through the B7-CD28 pathway for full activation [15]. More studies are needed to clarify practices that are perceived to attenuate these known risks.

4. Conclusions

This is the first case of PML described in the literature in a lung transplant recipient after initiation of standard dose Belatacept. Belatacept use in lung transplant recipients is an evolving therapy in immunosuppression management. Due to its success in renal transplant recipients for CNI sparing immunosuppression, it has gained popularity in use for lung transplant recipients. Its use has been associated infections, particularly viral infection, and post-transplant lymphoproliferative disorders. More studies are needed to clarify the relationship between Belatacept and risk of infection.

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CRediT authorship contribution statement

Vahdatpour C: Conceptualization, Writing – original draft, Writing – review & editing. **Saha B:** Conceptualization, Supervision, Writing – review & editing. **Younis M:** Conceptualization, Writing – review & editing. **Montuoro C:** Project administration, Writing – review & editing. **Timofte I:** Conceptualization, Supervision. **Rackauskas M:** Supervision, Validation. **Emtiazjoo A:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

None of the authors have conflicts of interests to declare.

Abbreviations

APCantigen presenting cell.
CNIcalcineurin inhibitor.
CTLA4cytotoxic T-lymphocyte-associated antigen 4.
PMLprogressive multifocal leukoencephalopathy.
PTLDposttransplant-lymphoproliferative disorder.

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