Enhancing Brain Lesions in a Renal Transplant Patient

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Abstract

Neurologists should be familiar with the spectrum of central nervous system (CNS) pathology that renal transplant patients are prone to. We are presenting a case of posttransplant lymphoproliferative disorder of the CNS to highlight less commonly described imaging findings and review this disease entity.

Keywords

renal transplant, central nervous system infection, posttransplant lymphoproliferative disorder (PTLD), primary central nervous system PTLD (PCNS-PTLD), brain neoplasms

Introduction

Renal transplants comprise the largest number of organ transplants; there were over 15 000 renal transplants in the United States in 2009.¹ This, plus the fact that renal transplant recipients have the highest 1- and 5-year survival rates, means neurologists will encounter such patients.¹ A thorough differential for central nervous system (CNS) symptoms in renal transplant patients includes ischemia, infection, immunosuppressant medication side effects, malignancy, seizures, and less commonly graft versus host complications. Keeping this differential broad is important since the results of serum, cerebrospinal fluid (CSF), and imaging may show atypical patterns in the immunosuppressed population. Here, we present a case of a renal transplant patient who presented with altered mental state and enhancing brain lesions on magnetic resonance imaging (MRI).

Case Description

A 48-year-old Hispanic male with a history of renal transplant was brought to the emergency room with a 2-week history of slowly worsening confusion, dysarthria, and a new right facial droop. On questioning, the patient complained of intermittent headache, although he was unable to state the duration or quality. There were no other neurological symptoms reported. His past medical history included a renal transplant 17 years prior; the suspected etiology for his renal disease was microscopic polyangiitis. He rejected the transplant 10 years later, was placed on hemodialysis, and received a second transplant 17 months prior to this admission. He also had a history of hypertension, diabetes, herpes zoster at the thoracic level, and a

positive purified protein derivative test for which he did receive treatment. His medications included tacrolimus, mycophenolate, prednisone, pyridoxine, aspirin, and verapamil. There was no significant family or social history other than that he had revisited his home country of Mexico 2 years prior.

On admission, his temperature was normal, blood pressure 110/70 mm Hg, heart rate 62 per minute, and oxygen saturation 98% on room air. He was lethargic, without meningismus, and had a normal cardiac, lung, skin, and lymphatic examination. Neurologic examination showed that he was oriented to self but not to place and that he needed to be aroused during the examination. The cranial nerve abnormalities included mild right facial droop and dysarthria, with the tongue being midline. The other cranial nerves were normal, along with the motor, sensory, and reflex examination; coordination and gait testing were not specifically mentioned on the outside hospital records.

Basic laboratories including blood count, chemistry, liver function, and coagulation studies were normal. An MRI scan of the brain with gadolinium revealed more than 15 supratentorial-enhancing lesions, most originating in the subarachnoid space but also invading the gray matter

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Figure 1. Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain. A, Axial postcontrast. B, axial T2. C, Diffusion-weighted images. D, Apparent diffusion coefficient images. The patient had multiple peripherally enhancing lesions (A). The lesions were predominantly extra-axial; however, they also appeared to invade the cortex. Extensive T2 hyperintensity surrounded the lesions, representing edema (B). The lesions had restricted diffusion (C, D).

(Figure 1). The lesions demonstrated restricted diffusion. There was no subependymal enhancement, and the ventricles were normal. The basal ganglia were also unremarkable. The initial differential diagnosis focused on infectious processes including *Coccidiomycosis*, *Cryptococcosis*, and *Cysticercosis*. Cerebrospinal fluid analysis showed an opening pressure of 11 cm of water, with clear fluid, white blood cells (WBCs) of $5 \times 10^9/L$, no red blood cells, glucose of 65 mg/dL, and an elevated protein of 85 mg/dL. Further serum and CSF testing were performed (Table 1). Chest radiograph and a computed tomography scan with contrast of the abdomen and pelvis were negative for masses.

The patient was started on dexamethasone, given the concern for mass effect; this led to improvement in his mental status over the next 3 days, and he was transferred to our hospital for a right frontal lobe stereotactic biopsy. Pathologic

examination revealed atypical lymphohistiocytic and plasma-rich proliferation, and there were many cells that stained positive for Epstein-Barr virus (EBV)-encoded ribonucleic acid (RNA) by in situ hybridization (Figure 2). The initial treatment plan was to discontinue the mycophenolate and taper the tacrolimus. Six days post biopsy, the patient had a subdural hemorrhage and underwent evacuation of the bleed. He was minimally arousable, had several seizures, and over several weeks he developed severe multiorgan failure prior to the family deciding to withdraw care.

Discussion

We presented a patient with primary CNS posttransplant lymphoproliferative disorder (PCNS-PTLD). The lesions of PTLD range from early lymphoid proliferations to malignant

Table 1. Serum and Cerebrospinal Fluid (CSF) Testing

Laboratory Test	Patient Value
Serum Results	
HIV PCR	Negative
<i>Toxoplasmosis</i> IgM Ab and PCR	Negative
<i>Cryptococcal</i> Ag	Negative
<i>Coccidioides</i> IgG/IgM Ab	Negative
CMV PCR	Negative
EBV PCR	Negative
EBV capsid IgM Ab	Negative
EBV capsid IgA Ab	>749.9 elevated ^a
EBV early antigen IgG Ab	>149.9 elevated ^a
EBNA	>599.90 elevated ^b
Flow cytometry	Negative
CSF results	
<i>Cryptococcal</i> Ag	Negative
<i>Acid fast bacillus</i> stain and PCR	Negative
India ink	Negative
Bacterial, fungal, mycobacterial cultures	Negative
Flow cytometry	Negative
Cytology	Negative

Abbreviations: HIV, human immunodeficiency virus; PCR, polymerase chain reaction; IgM, immunoglobulin M; Ab, antibody; Ag, antigen; CMV, cytomegalovirus; EBV, Epstein-Barr virus; EBNA, Epstein-Barr virus antibody to nuclear antigen, IgG.

^a Exact reference ranges not available.

^b Patient's EBV status at the time of transplant is not known.

lymphomas with 80% to 90% of the cases being associated with EBV infection.² Rates of PTLT are highest in the first year following transplant, but the increased risk of lymphomatous disease remains lifelong compared to the general population.² The incidence varies by transplant type, ranging from 0.6% to 2.5% for kidney transplant recipients to as high as 20% for small bowel transplant recipients.³ Involvement of the CNS is relatively uncommon, with incidence usually reported between 5% and 30% of PTLT cases.^{2,4} In many of these cases, the CNS is the only area involved, earning the name PCNS-PTLT.^{2,4} Neurological symptoms in PCNS-PTLT are nonspecific and include altered mental status, headache, and focal neurological symptoms.⁴

The pathogenesis of PTLT is thought to be related to the EBV-infected memory cells transforming into clonal populations because the cytotoxic T-cell activity that usually responds to the B-cell proliferation is suppressed in transplant patients.² The World Health Organization uses pathologic findings to classify the lesions into early, polymorphic, and monomorphic lesions, which includes B-cell neoplasms such as diffuse large B-cell lymphoma or Burkitt lymphoma.⁵

The workup of our patient was similar to that of most renal transplant patients presenting with neurological symptoms and started with imaging. Given our case's imaging revealed multiple enhancing brain lesions, many of which were in the subarachnoid space, both stroke and posterior reversible encephalopathy syndrome were excluded as differential considerations. Infectious etiologies were high on the differential in our patient. Key organisms to consider in renal transplant patients

with enhancing brain lesions include *Aspergillus*, *Nocardia asteroides*, *Toxoplasma gondii*, *Listeria monocytogenes*, *Mucorales*, *Tuberculosis*, and less commonly *Cryptococcus*.⁶ The major noninfectious causes of enhancing brain lesions in renal transplant patients are PCNS lymphomas, PCNS-PTLT, and metastatic disease.

The more commonly described radiographic findings of PCNS-PTLT that were seen in our case include multicentric disease, heterogeneous lesion enhancement, and a lack of leptomeningeal and ependymal enhancement.^{4,7,8} Reviews on PCNS-PTLT cite that the lesions are usually found in the deep supratentorial structures, including the periventricular region and the subcortical white matter.⁸ Similarly, case series reported that such lesions were commonly found located in the basal ganglia followed by the frontal lobe.^{4,9} Interestingly, most of our patient's lesions had their epicenter in the subarachnoid space. This finding does not appear to be commonly described in other PCNS-PTLT cases, with the exception of one series that highlighted the ependymal predisposition of lesions.⁹ Many published cases of PCNS-PTLT do not comment on the specific number of lesions, but in the publications that do, typically 1 to 4 lesions are seen with a select number of cases describing 5 to 9.^{4,10-12} It is notable that our patient's MRI demonstrated such a large lesion number (greater than 10), in a range usually appreciated with CNS infections or metastatic disease.

As with imaging, there are no highly sensitive or specific serum and CSF tests to help make the diagnosis of PCNS-PTLT. Although there is one study supporting the use of plasma EBV polymerase chain reaction (PCR) testing as a way to make an early diagnosis of PTLT in adults; this has not been established in patients with PCNS-PTLT.¹³ Despite our patient's positive EBV early antigen test, we think his other EBV serologies were most suggestive of a prior infection; the early antigen test may persist in up to 20% of people with prior EBV infection.¹⁴ Our patient's CSF profile was mainly helpful in placing infectious etiologies lower on the differential, although even this conclusion is made with caution given his immunosuppressed state. From the largest case series of PCNS-PTLT patients, median CSF WBC count was $12 \times 10^9/L$, and median CSF protein was 79 g/L.⁷ The CSF cytology was positive in 1 out of 20, and flow cytometry was positive in only 1 out of 12 lumbar punctures.⁷

With regard to treatment in either PCNS-PTLT or PTLT, currently there is no standardized regimen. It is generally proposed to first try reducing immunosuppression and reassess after several weeks; however, groups have shown that many of these patients require additional therapy.^{4,7} Treatment regimens include, but are not limited to, anti-B-cell therapies, methotrexate, chemotherapy regimens, and whole brain radiation. Case series with variable treatment regimens report median survival rates ranging from 7 to 36 months.^{7,15}

In summary, this case highlights a disease that is still relatively uncommon but one that neurologists will encounter

Figure 2. Brain biopsy. Representative photomicrographs of the brain stained with H&E (A), CD20 immunohistochemistry (B), CD138 immunohistochemistry (C), and stained with EBV-encoded RNA in situ hybridization (EBER ISH). The lesion shows mixed infiltrates of small lymphocytes and plasma cells in the angiocentric distribution. Extensive necrosis and marked reactive astrogliosis are noted. CD20 highlights scattered B-cells within the lesion. CD138 highlights scattered plasma cells within the lesion. Many cells within the lesion are positive for EBV early RNA by in situ hybridization. H&E indicates hematoxylin and eosin; EBV, Epstein-Barr virus.

more frequently as the transplant population increases and survives longer. As this case demonstrates, we still are uncovering the spectrum of imaging findings associated with PCNS-PTLD, and therefore, it is important to have PCNS-PTLD on the differential in all transplant patients who present with CNS symptoms.

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