Mystery Case:

CNS posttransplant lymphoproliferative disorder

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SECTION 1

A 74-year-old right-handed Hispanic woman with history of renal transplant 19 years prior presented at an away institution with episodic confusion and gait ataxia progressing over 2 weeks. She was alert and oriented on initial presentation but with fluctuation in mental status and without obvious cranial nerve, motor, or sensory deficits. The patient received transplant immunosuppression therapy with mycophenolate mofetil (Cellcept; Roche, Basel, Switzerland) and had a history of hypertension and chronic kidney disease. CT of the head showed a hypodense lesion in the right temporal lobe. MRI of the brain demonstrated multifocal, infiltrative T2-hyperintense white matter lesions involving the right temporo-parietal region, right frontal lobe, left parietal lobe, and left thalamus (figure, A–C). Gadolinium was not administered due to renal dysfunction. Lumbar puncture (LP) showed 63 leukocytes with lymphocytic pleocytosis (88%), elevated protein (80 mg/dL), and normal glucose (71 mg/dL). CSF Gram stain and culture were negative. She was treated with corticosteroids and acyclovir for presumed autoimmune/demyelinating vs infectious etiologies. She developed multiple witnessed periods of behavioral arrest with eye blinking and confusion

concerning for seizures. She was transferred to our institution.

On examination, the patient was somnolent, disoriented, and intermittently followed commands. Cranial nerve examination was normal. She localized to pain and moved all 4 extremities spontaneously with at least 3/5 motor strength. She had increased tone with hyperreflexia throughout, nonsustained ankle clonus, and extensor plantar reflexes bilaterally. Gait, coordination, and sensations could not be assessed.

Continuous EEG showed right temporal sharp waves and 8- to 20-second epochs of bifrontal 14–18 Hz activity, some of which were associated with nonstereotyped movements of her left shoulder and trunk, concerning for status epilepticus. She was treated with IV benzodiazepines followed by a load of phenytoin (Dilantin; Pfizer, New York, NY) and renal dosing of levetiracetam (Keppra; UCB, Brussels, Belgium), which controlled her seizures.

Questions for consideration:

1. What is the differential diagnosis?
2. What are the next steps toward a definitive diagnosis?

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**Supplemental data
at Neurology.org**

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(A-C) MRI of brain obtained during initial presentation. Axial fluid-attenuated inversion recovery (FLAIR) images demonstrate T2 hyperintense lesions involving the right frontal (A), right parieto-occipital (A, B), left thalamus and parieto-occipital (B) regions and a large infiltrative T2 hyperintense lesion involving the right temporal lobe (C). FLAIR sequence from MRI obtained 2 months after initial imaging following treatment with immunosuppression reduction, sirolimus, and rituximab infusions demonstrates radiographic improvement and a resolving right temporal lobe lesion (D). (E-H) Histopathology of polymorphic PTLD. Hematoxylin & eosin-stained sections demonstrate partially necrotic tissue with a polymorphous lymphoid aggregate composed of granulocytes, lymphocytes, and small mature plasma cells (E, $\times 40$ magnification). Lymphocytes demonstrate a mixture of CD3-positive T cells (F, $\times 20$ magnification) and CD20-positive B cells (G, $\times 20$ magnification). Immunohistochemical studies for EBV (latent membrane protein-1 [LMP-1]) stain positive in a predominantly cytoplasmic pattern (H, $\times 40$ magnification). LMP-1 staining is seen predominantly within B immunoblasts.

SECTION 2

Brain lesions among immunosuppressed patients pose a diagnostic challenge; differential diagnoses include infections, demyelination, and neoplastic etiologies (table e-1 at Neurology.org). The patient was further evaluated with brain imaging, LP, blood tests, and brain biopsy. Findings on repeat CSF examination and other results are shown in table e-2. Epstein-Barr virus (EBV) DNA was detected in CSF on qualitative PCR; blood EBV viral load test (PCR for the detection of the EBV gene Epstein-Barr nuclear antigen-1) resulted 1,458 copies/mL. MRI brain was repeated 12 days after transfer and showed unchanged appearance of previously described lesions. A stereotactic right temporal brain biopsy was performed. Hematoxylin & eosin–stained histologic sections demonstrated partially necrotic tissue with a polymorphous lymphoid aggregate composed of granulocytes, lymphocytes, and small mature plasma cells (figure, E). Plasma cells were shown to be polytypic for kappa and lambda light chains. Lymphocytes demonstrated a mixture of CD3-positive T cells (figure, F) and CD20-positive B cells (figure, G), which also were positive for CD30 in areas. Immunohistochemical studies for EBV latent membrane protein-1 (LMP-1) were positive in a predominantly cytoplasmic pattern (figure, H).

Epstein-Barr encoding region in situ hybridization was performed using chromogenic assays on formalin fixed paraffin embedded tissue, and was focally positive. These findings supported a diagnosis of polymorphic posttransplant lymphoproliferative disorder (PTLD) by the 2008 WHO criteria for classification of tumors of hematopoietic and lymphoid tissues.

Mycophenolate was discontinued, and the patient was acutely treated with dexamethasone (Decadron, Merck, Kenilworth, NJ), which was later discontinued. She received 6 infusions of rituximab (Rituxan; Biogen, Cambridge, MA) and treatment with sirolimus (Rapamune; Pfizer), which resulted in negative EBV viral serology and improvement in alertness and cognitive function with resolution of brain lesions on MRI over 1 to 3 months (figure, D). She could follow commands appropriately, but was frail, with minimal strength against resistance in all extremities. Her clinical condition precluded cellular immune therapy with EBV-targeted cytotoxic T lymphocytes (CTLs).

Questions for consideration:

1. What is PTLD and how frequently does it involve the CNS?
2. How does one differentiate CNS-PTLD from primary CNS lymphoma?

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SECTION 3

We describe a case of primary CNS-PTLD as a complication of renal transplantation. PTLD is a potentially fatal complication among recipients of solid organ transplant (SOT) and hematopoietic stem cell transplant. Its incidence varies from 1% to 5% after liver and renal transplantation to a higher incidence among multiorgan transplant recipients (up to 20%–25% absolute risk in some series).¹ While 15% of patients with PTLD can have CNS involvement, primary CNS-PTLD is rare.² According to the WHO Global Observatory on Donation and Transplantation, 1.2 million SOTs were performed between 2000 and 2014 worldwide; among them 66.5% (828,863) were renal transplants. Reports on incidence of PTLD and CNS-PTLD among recipients of different SOTs have to be weighed against the fact that renal transplants are the most common SOT performed worldwide and heterogeneity of patient data. Time from transplantation to diagnosis of CNS-PTLD can range from 12 to 24 months to a delayed presentation occurring >10 years; a median time of 4.5 years is reported in 2 large case series.^{3–5}

Other risk factors include the type/intensity of immunosuppression used. PTLD has been reported after the use of prednisone, azathioprine (Imuran; Prometheus, San Diego, CA), cyclosporine (Neoral; Novartis, Basel, Switzerland), tacrolimus (Prograf; Astellas, Northbrook, IL), mycophenolate mofetil, and monoclonal antibodies used for induction therapy such as OKT3 (Muromonab-CD3; Janssen Biotech, Horsham, PA). Incidence of PTLD appears to be related to total burden of immunosuppression, rather than the nature of individual agents.

WHO classifies PTLD into 4 histopathologic types: (1) early lesions, (2) polymorphic PTLD, (3) monomorphic PTLD, and (4) classic Hodgkin lymphoma-type PTLD.⁶ This disorder most commonly affects B cells, although infrequently it can affect T cells. Primary infection of a previously EBV-seronegative patient during immunosuppression is a risk factor for PTLD. Nearly 90% of cases are seropositive for EBV.⁴ The monomorphic subtype includes neoplasms that are morphologically and immunophenotypically indistinguishable from conventional lymphomas. The constellation of findings including necrosis, polymorphous lymphoid population including polytypic plasma cells, and EBV positivity in the setting of transplant and immunosuppression supports a diagnosis of polymorphous PTLD as opposed to monomorphic subtype. Immunohistochemistry in our patient was positive for expression of CD30, which can be detected in all types of PTLD and is shown to correlate with favorable outcomes.⁷ CD30 antigen is potentially targetable, with the monoclonal antibody brentuximab vedotin (Adcetris; Seattle Genetics, Bothell, WA).

Clinical features of CNS-PTLD include headache, hemiparesis, ataxia, aphasia, impaired mentation, and seizures. Lesions are usually contrast-enhancing. Homogenous, heterogeneous, and ring enhancement have been described.³ While lobar lesions are most common, meningeal, basal ganglia, periventricular, infratentorial, and spinal cord lesions can also occur. The majority of patients present with multifocal brain lesions.^{3,5,8} Ocular involvement is rare.⁴ Differential diagnoses for PTLD and their diagnostic workup are shown in table e-1. CSF studies can be nonspecific, with pleocytosis and elevated protein but with negative cytology and flow cytometry.³ EBV PCR can be negative in the serum, but usually positive in CSF. Distinguishing the lesions of CNS-PTLD from CNS lymphoma and infections requires cerebral biopsy. Histologically, monomorphic PTLD is most common, with the majority of disease arising from a B-cell lineage that has a detectable EBV genome.^{3,4,8}

Measures to reduce the risk of PTLD include limiting the dosage and number of immunosuppressive medications, prophylactic antiviral medications, and immunoglobulin. A systematic review of 31 studies showed no significant difference in the rate of EBV-associated PTLD among SOT recipients who received prophylaxis (with acyclovir, ganciclovir, valganciclovir, or valganciclovir), compared to those receiving no prophylaxis.⁹ A large retrospective study showed reduced short-term (within 1 year) incidence of PTLD with use of anticytomegalovirus immunoglobulin after renal transplant, but no difference long-term.¹⁰

Treatment involves immunomodulation and chemotherapy with or without radiotherapy, with a concurrent goal of preserving allograft function. First-line therapy consists of reducing immunosuppression, which can induce remission in 50% of patients with systemic PTLD.^{1,8} Adoptive immunotherapy is a strategy aimed at restoring cell-mediated immunity, by administering EBV-specific CTLs that are selected and expanded *ex vivo*.^{1,8} Considering the time required for generation of autologous CTLs, this strategy may not be applicable in rapidly progressive forms of CNS-PTLD. Systemic chemotherapy with methotrexate (Trexall; Teva, Petah Tikva, Israel) or rituximab, though associated with lower response rates than with radiotherapy, can result in good radiographic responses in CNS-PTLD.⁴ Higher response rates and improved survival are reported among patients who receive radiotherapy with or without chemotherapy.³ Although CNS involvement confers a poor prognosis among patients with PTLD, a median survival of 47 months was reported in one series.³

PTLD should be considered in patients presenting with new-onset neurologic symptoms and with

a history of solid organ or bone marrow allograft transplantation with posttransplant immunosuppression. CNS-PTLD is a distinct clinicopathologic subset within the PTLD spectrum that can occur late, has monomorphic histology with strong EBV positivity, and with neuroimaging features that overlap with primary CNS lymphoma. Distinction lies in clinical history, features on biopsy, response to therapy, and clinical outcomes.

AUTHOR CONTRIBUTIONS

Drs. Kesari, Kapadia, and Chen: acquisition of data and writing the initial drafts of the manuscript. Dr. Blieden: preparation and writeup on histopathology slides. Dr. Sivakumar: study concept, design, and writing final drafts of the manuscript. Drs. Venkatasubba Rao and Suarez: critical revision of manuscript for intellectual content.

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MYSTERY CASE RESPONSES

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group e-mail sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media. We received 459 responses. The majority of respondents (70%) had just been in practice for 1–4 years; 58% were residents/fellows while 31% were faculty/board-certified physicians. Sixty-six percent resided outside the United States. A wide range of practice settings was represented.

With respect to the neuroimaging findings on MRI brain for this patient, 68% of the respondents correctly identified the right frontal hyperintense lesion and associated periventricular hyperintensities, and 64% identified the right occipital lobe lesion. Perhaps reflecting a satisfaction-of-search, a smaller proportion (52%–54%) also identified the large right temporal lobe and right parietal lobe hyperintense lesion, and left thalamic lesion, while only 38% also identified the left parietal hyperintense lesion. Upon being given information about the patient's clinical presentation, medical history (kidney transplant and immunosuppression) examination findings, initial lumbar puncture results, and EEG findings, and asked to select their top 3 differential diagnoses, 71% chose progressive multifocal leukoencephalopathy (PML), 57% chose viral/chronic infectious encephalitis, and 39% chose PTLD. These were our recommended answers given the patient's subacute confusion/ataxia/seizures and immunosuppression. Autoimmune/paraneoplastic encephalitis (44%), acute disseminated encephalitis (27%), and posterior reversible encephalopathy syndrome (PRES; 26%) were other popular choices. These are also appropriate considerations in subacute encephalopathic presentations; although autoimmune presentations could be considered less likely in an immunosuppressed patient, immunosuppression and renal disease as seen in this patient are both risk factors for PRES (which despite the name is not always posterior).¹

After being informed about the patient's lack of response to corticosteroids and acyclovir, negative antibody testing, and negative JC virus (expected

to be positive in PML),² but positive EBV DNA in the CSF, and asked about next steps, 38%–39% appropriately chose to stop corticosteroids and mycophenolate mofetil, and pursue brain biopsy to establish the diagnosis. Forty-one percent also chose to continue acyclovir; this is a reasonable choice with an uncertain presentation but needs careful thought about risk vs benefit in someone like this patient with chronic kidney disease. Finally, upon being shown the biopsy findings, 46% chose the diagnosis of EBV encephalitis, whereas 18% chose primary CNS lymphoma (PCNSL) and 17% chose the diagnosis of PTLT. Practically speaking, both PCNSL and PTLT are correct (indeed the 2010 report on primary CNS-PTLT was put together by the PCNSL collaborative group).³ PTLT is perhaps a more specific term for this case as it recognizes that this lymphoma is in a posttransplant patient. It would seem that in selecting EBV encephalitis, most respondents were overly influenced by the histologic finding of cytoplasmic EBV LMP-1 positivity in the biopsy specimen. However, strong EBV positivity is a key feature of CNS-PTLT, and primary infection in a previously EBV-seronegative patient during immunosuppression is actually a risk factor for PTLT, with 90% of cases seropositive for EBV.⁴ Whereas necrosis (as seen in this case) is certainly seen in viral encephalitis, and viral encephalitis can rarely present with multiple mass lesions radiologically resembling lymphoma, histopathology would typically be characterized by cellular perivascular T-cell infiltrates of low to moderate proliferative activity, occasional microglial nodules, and neuronophagia.⁵ We would not expect to see the polymorphic tumor cells seen in this biopsy.

This case and its responses illustrate a number of relevant teaching points: the approach to subacute encephalopathy or cerebral lesions in an immunosuppressed patient, the importance of systematically reviewing neuroimaging findings especially in the presence of an obvious large lesion to avoid missing more diffuse processes, the challenges of differentiating CNS manifestations of EBV, and the fact that PTLT can be a delayed presentation more than a decade after transplantation.

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