Clinical Reasoning: Agitation and psychosis in a patient after renal transplantation

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SECTION 1

A 31-year-old woman was admitted for fever and altered mentation of unclear etiology 16 months after a renal transplant. This was her third admission in 4 months for fever of unclear etiology, but the current admission differed in that she also demonstrated short-term memory loss, dramatic mood swings, agitation, and paranoid delusions. Other significant medical history included non-Hodgkin lymphoma in childhood for which she underwent 2 allogeneic stem cell transplants,

chemotherapy, and whole-body radiation. She also developed postradiation kidney failure which necessitated a cadaveric kidney transplant followed by immunosuppression with tacrolimus 2 mg BID and mycophenolate 1 g BID.

Questions for consideration:

1. What is the most likely etiology of rapid onset altered mental status and fever in the context of immunosuppression?
2. What are the initial tests to consider for this etiology?

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SECTION 2

In any patient on immunosuppression with fever and altered mentation, an infectious etiology is of primary concern. MRI of the brain with contrast did not reveal any abnormalities. Her CSF showed 0 RBC/ μ L (normal 0), 19 WBC/ μ L (normal 0–5) with 96% lymphocytes and 4% monocytes, glucose 42 mg/dL (normal 50–80), protein 144 mg/dL (normal 15–60). An extensive infectious workup including chest x-ray, blood culture, urine culture, HIV serology, acid-fast bacilli, varicella zoster virus PCR, fungal antigen testing, *Toxoplasma gondii*, Lyme serology, cytomegalovirus, western

equine immunoglobulin G (IgG)/immunoglobulin M (IgM), West Nile virus antibody, human herpesvirus 6, rapid plasma reagin, herpes simplex virus 1 and 2, and cryptococcal antigen were all negative.

Questions for consideration:

1. What is the differential diagnosis for altered mentation in this immunosuppressed patient with mild lymphocytic pleocytosis and negative infectious workup?
2. What additional workup should be considered at this time?

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SECTION 3

Encephalopathies secondary to neoplastic, paraneoplastic, seizure, toxic, autoimmune, or metabolic etiologies were considered. Workup for occult malignancy including CSF cytology, SPEP/UPEP, and an extensive paraneoplastic panel were negative. A body PET scan identified a left iliac crest hypermetabolic area, which biopsy showed no evidence of malignancy. Seizures were also considered but her EEG during episodes of confusion showed normal EEG for age. Complete blood cell count, blood and urine chemistry, B12/folate, thyroid-stimulating hormone/FT4, antineutrophil cytoplasmic antibodies panel, angiotensin-converting enzyme level, and urine drug screen were also within normal limits. All symptoms spontaneously resolved during this third admission.

Three weeks later she was readmitted for recurrent agitation, paranoid delusions, and persistent tachycardia. Tacrolimus level was 5 ng/mL (normal 6–15) and mycophenolate level was 3 µg/mL (normal 1–3.5) at the time of admission. Repeat infectious workup was negative except for positive Epstein-Barr virus (EBV) PCR in the CSF and positive serum EBV IgM and IgG antibodies with negative EBV nuclear antibodies. These findings suggested infectious mononucleosis. BK virus PCR was positive in urine and serum but her renal biopsy was negative for BK virus nephropathy. Over the next week she developed worsening psychosis and was treated for possible EBV encephalitis with ganciclovir. Because of her BK viremia and possible EBV encephalitis there was concern that she was overimmunosuppressed, although her CD4-ATP immune cell function was in the moderate function level. In consultation with her nephrologist, mycophenolate was discontinued and tacrolimus dose was decreased.

Over the next 2 weeks she lapsed into catatonia with diffuse muscle rigidity, waxy flexibility, persistent tachycardia, and hypotension necessitating transfer to the intensive care unit (ICU). These symptoms only partially improved with high doses of benzodiazepines and antipsychotic medications including olanzapine, aripiprazole, and quetiapine. Repeat EEG did not show epileptic activity and repeat brain MRI was unchanged. Due to her presentation of encephalopathy with prominent psychiatric features and autonomic instability, anti-NMDA receptor (NMDAR) encephalitis was considered.

Antibodies to NMDAR were identified in her CSF (titer 1:10) and no antibodies were detected in serum. She was started on a course of methylprednisolone 1 g IV daily for 5 days and then prednisone 60 mg PO daily. Within 5 days of starting steroids

the catatonia markedly improved. Over the next 2 months her condition gradually improved with only mild residual memory deficits and behavioral disinhibition. She was continued on oral steroids and had a very gradual taper over 15 months. Extensive workup to identify an underlying neoplasm was negative. An examination by gynecology-oncology, pelvic ultrasound, pelvic MRI, and whole-body PET were negative.

After 6 months of outpatient rehabilitation she was able to return to her job full time. Repeat brain MRI and body PET scan 6 months after discharge did not demonstrate evidence of neoplasm. Lumbar punctures were done at intervals during her recovery and demonstrated a slow decline in anti-NMDAR antibody titer and at discontinuation of steroids were no longer detectable in the CSF. She has had no relapse of symptoms for more than a year.

Question for consideration:

1. What is the mechanism for this individual's anti-NMDAR encephalitis in the context of immunosuppression?

DISCUSSION The recent elucidation of a reversible encephalopathy with prominent memory deficits, psychosis, dyskinesias, and autonomic instability has been linked to antibodies to the NMDARs. In about 50% of patients older than 18 years an underlying neoplasm is identified, usually an ovarian teratoma, which on biopsy shows neuronal tissue.^{1,2} These patients produce antibodies against the extracellular NR1 subunit of the NMDAR.² This encephalopathy tends to affect young females, although children, the elderly, and men are also affected.

In vitro and in vivo studies show that these antibodies produce a reversible decrease of cell surface density and synaptic localization of NMDAR clusters via antibody-mediated capping and internalization of the receptors.³ The reversible nature of the decrease of NMDAR and lack of cell death explains the frequent reversibility of symptoms even with severe clinical presentations. Patients in acute phases of this disorder also have higher antibody titers and intrathecal antibody synthesis compared to the titers during the recovery phase. NMDAR dysfunction has been implicated in schizophrenia. Phencyclidine and ketamine, both noncompetitive antagonists of NMDAR in humans, cause psychiatric and cognitive dysfunction, and stereotyped movements similar to those seen in anti-NMDAR encephalitis.^{4,5}

Our patient is unique in several aspects. First, she developed this autoimmune disorder while already on immunosuppression, in this case for kidney transplant. She was on therapeutic and standard doses of both tacrolimus and mycophenolate when symptoms

developed. Mycophenolate impairs lymphocyte function by blocking purine biosynthesis via inhibition of inosine monophosphate dehydrogenase. This inhibits de novo guanosine nucleotide synthesis upon which both T and B lymphocytes rely. Tacrolimus suppresses cellular immunity by inhibiting T-cell activation by binding to an intracellular protein to inhibit calcineurin phosphatase activity. As anti-NMDAR encephalopathy is believed to develop by complement-independent antibody effects it would seem counterintuitive that an autoimmune disorder could occur in the setting of immunosuppression. However, this is a well-known problem in patients with postallogeic stem cell transplant, usually those having graft-vs-host disease. For example, some of these patients have propensity to develop autoimmune processes such as polymyositis, myasthenia gravis, and Guillain-Barré syndrome.⁶

Although the detection of BK viruria and viremia suggested that the patient was overimmunosuppressed, leading to decrease of immunosuppressants by her nephrologist,⁷ a longitudinal study in 104 renal transplant patients showed that up to 57% and 29% of post renal transplant patients develop BK viruria and BK viremia, respectively.⁸ Her BK viruria and viremia may not have truly indicated overimmunosuppression but rather an expected finding after her transplant. Moreover, after decreasing her immunosuppression she clinically worsened and required transfer to the ICU. This, along with her normal lymphocyte functional tests, suggests that despite appearances she was inadequately immunosuppressed until use of IV steroids, which has better CNS penetration than her oral immunosuppressants. This is supported by both her clinical improvement and the progressive decrease of CSF antibody titers over 15 months while on steroids (1:10 to 1:2, to undetectable).

It is also of interest that the patient was found to have EBV virus suggestive of mononucleosis and her initial presentation of fever and fatigue was consistent with this diagnosis. Whether this was the first indication of activation of the immune system or her immunosuppression regimen causing her to have reactivation of EBV is impossible to tell at this point. Additionally, having a viral infection, specifically EBV may have increased blood-brain barrier (BBB) permeability. A recent study shows that EBV can infect the human BBB cells leading to increased production of proinflammatory mediators. These mediators could result in immune cell adherence leading to neuronal dysfunction.⁹ This patient highlights the very complex immunologic interactions that contribute to the development of nonparaneoplastic anti-NMDAR encephalitis. Moreover, it also suggests that anti-

NMDAR encephalitis may result from autoimmune mechanisms that are not specifically suppressed by mycophenolate and tacrolimus. Even in post-transplant or other patients on immune-modulatory therapy the diagnosis of anti-NMDAR encephalitis should be considered when the clinical picture suggests this disease. The role of a viral prodrome either from a primary infection or viral reactivation as a trigger of the encephalitis also makes the balance of the immune-modulatory medication in these patients more difficult.

AUTHOR CONTRIBUTIONS

Cong Zhi Zhao: contributed to the study design, drafting/revising the manuscript for content, including medical, writing for content, and analysis or interpretation of data. Jay Erickson: contributed to the study design, drafting/revising the manuscript for content, including medical, writing for content, and analysis or interpretation of data. Josep Dalmau: contributed to drafting/revising the manuscript for content, including medical writing for content and analysis or interpretation of data.

DISCLOSURE

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