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Mania Associated With Supratherapeutic Tacrolimus Levels in a Patient With No Psychiatric History

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Introduction

Calcineurin inhibitors have long been a cornerstone for post-transplant immunosuppressive treatment. Calcineurin inhibitors are known to produce neurotoxic side effects such as headaches, tremors, and paresthesias.1,2 This is also true for tacrolimus, which is more potent than other calcineurin inhibitors and has a narrow therapeutic window, resulting in a plethora of potential side effects, especially when levels become supratherapeutic.3 We conducted a literature review using PubMed and Google Scholar with an emphasis on the psychiatric side effects of tacrolimus. The only report of mania associated with tacrolimus involved a patient with a history of bipolar disorder.4 Other reports of psychiatric symptoms in patients with no psychiatric history are involved catatonia and paranoid delusions.5,6 To our knowledge, this is the first report of mania secondary to supratherapeutic tacrolimus levels in a patient with no psychiatric history. We present this case to demonstrate a temporal relationship between supratherapeutic tacrolimus drug levels and the development of a manic episode.

Case Report

Mr. A, a 64-year-old man with a history of congestive heart failure, chronic atrial fibrillation, hypertension, open-angle glaucoma, gout, chronic anemia, aortic insufficiency status after aortic valve replacement, end-stage renal disease status after kidney transplant in 2013, and had no psychiatric history. He had no prior use of psychotropics and reported no substance use in the last year. Home medications included allopurinol 100 mg daily, amiloride 10 mg, atorvastatin 40 mg nightly, latanoprost and timolol eye drops, bumetanide 2 mg twice daily, vitamin D, hydralazine 25 mg every 8 hours, metolazone 2.5 mg daily (3 times a week), metoprolol 50 mg daily, ferrous sulfate 324 mg daily, sildenafil 20 mg (1–2 pills daily as needed), tacrolimus 1 mg in the morning and 2 mg at night (since 5 y), prednisone 5 mg daily (since 5 y), everolimus 1 mg twice daily (since 16 months), and warfarin 5 mg for 4 days a week and 7.5 mg for 3 days a week. Sildenafil was the only new medication prescribed in the previous 2 months; no other medications were discontinued or adjusted to our knowledge.

Mr. A was taken to the emergency room by his family for acute behavioral changes. Two weeks before, without consulting the transplant clinic, he had made the decision to take extra tacrolimus pills higher than his prescribed dose after seeing that his tacrolimus levels were low on routine laboratory tests. Over the course of 10 days, his family noticed that he was irritable, hyperverbal, not sleeping, spending money without discretion, verbally aggressive, threatening to divorce his 40-year-old wife, and making grandiose statements about hosting lavish hotel parties and buying expensive cars.
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On assessment in the emergency room, he was belligerent and verbally aggressive. Physical examination was unremarkable except for irritable mood and pressured speech. Laboratory tests showed creatinine elevated at 3.10 mg/dL, blood urea nitrogen elevated at 77 mg/dL, and glomerular filtration rate low at 23 mL/min/1.73 m² (normal range is more than 60), as well as an elevated brain natriuretic peptide at 717 pg/mL. Everolimus level was notably subtherapeutic at 2.2 ng/mL (normal range, 3–19.9 ng/mL). The international normalized ratio was subtherapeutic at 1.37. The FK506 level, which is the test that measures tacrolimus in the blood, was elevated at 25.9 ng/mL (normal range, 5–19.9 ng/mL). The last FK506 level drawn was 15 days before and was 6.8 ng/mL. The patient’s FK506 levels in the previous year had ranged from 4.4 ng/mL to 8.6 ng/mL. For the previous 6 months, baseline creatinine ranged between 2.0 and 3.06 mg/dL and blood urea nitrogen level was between 71 and 118 mg/dL. The computed tomography of his head was negative for any acute processes but showed chronic small vessel ischemic changes consistent with his age. Other laboratory tests were negative/unremarkable (urinalysis, urine drug screen, liver function tests, ammonia level, magnesium, complete blood count, and thyroid stimulating hormone). On consulting with the renal transplant team, tacrolimus was discontinued owing to elevated FK506 levels, and Mr. A was admitted to the general medicine floor after which psychiatry and neurology were consulted to assist with diagnosis and management.

On assessment by the primary team on day 2, symptoms and physical examination were unchanged. The team gave him intravenous fluids to treat acute kidney injury thought to be secondary to tacrolimus toxicity and did not restart tacrolimus. The FK506 level trended down to 16.2 ng/mL. The creatinine level trended down to 2.85 mg/mL and blood urea nitrogen trended down to 71 mg/dL indicating that acute kidney injury was resolving.

The renal transplant team and neurology consult team examined Mr. A and found no physical or focal neurological deficits. Cerebrospinal fluid (CSF) analysis showed mildly elevated protein without pleocytosis but was otherwise unremarkable. The combination of protein and lymphocytes was not concerning for neurosyphilis. In addition, CSF was negative for the West Nile virus, West Nile immunoglobulin G antibody, and West Nile immunoglobulin M antibody. The magnetic resonance imaging (MRI) scan was negative for posterior reversible encephalopathy syndrome and multiple sclerosis; the MRI of the brain showed chronic mild white matter disease and T2 hyperintensity in the centrum ovale, slightly more than the MRI from 2007 with no evidence of acute process, age-appropriate atrophy without hydrocephalus, and a tiny focal area of encephalomalacia in the left frontal lobe which is stable and may relate to prior trauma.

On day 3, the renal transplant team recommended restarting tacrolimus at 1 mg twice daily; however, by day 5, it was discontinued again because of ongoing mania. The renal transplant team and neurology consult team did not believe his behavior could be explained by the MRI changes, an acute infectious process, or acute vascular phenomenon and collectively agreed that the presentation was likely due to tacrolimus toxicity.

The psychiatry team saw Mr. A on day 2, and a mental status examination showed he was alert and oriented to person, place, and time, with intact sensorium. He had an irritable mood, labile affect, rapid and pressured speech, loose associations, flight of ideas, lack of need for sleep, hyperverbal speech, grandiose thoughts of wanting to host a party “in the largest conference room” at a famous hotel, wanting to “purchase 16 properties before my 65th birthday,” paranoia that he was poisoned by the hospital or by his wife for health insurance money, and impulsivity by verbalizing that he wanted to divorce his wife. A formal cognitive screen was not possible owing to lack of cooperation. The psychiatry team recommended starting olanzapine 2.5 mg twice daily and titrated to 5 mg twice daily by day 3. On day 5, he showed some improvement, but owing to persistent symptoms, valproic acid was added at 500 mg twice daily. On day 7, Mr. A began complaining of new onset blurry vision, so olanzapine was reduced to 5 mg nightly because of potential anticholinergic side effects, and valproic acid was titrated to 750 mg twice daily.

By day 8, the FK506 levels trended down to 2.5 ng/mL. The acute kidney injury had also resolved with creatinine returning to 2.0 mg/dL and blood urea nitrogen to 43 mg/dL, which though still elevated, was close to baseline for this patient. Ultimately, the
Calcineurin inhibitor–induced neurotoxicity is a well-established phenomenon, and the package insert for tacrolimus lists psychosis and delirium as adverse effects. To our knowledge, this is the first case report of mania secondary to medication with tacrolimus in a patient with no psychiatric history.

The differential diagnosis for this presentation was wide ranging on multiple levels. First, there have been reports of steroid induced mania,\(^7\) so drug interactions were reviewed to see if tacrolimus or any other medications cause reduced prednisone clearance leading to accumulation of prednisone. An interaction check showed that there are no pharmacokinetic interactions between his 3 immunosuppressants and no other interactions relevant to this case. As prednisone is primarily excreted in the urine, it is plausible that the acute kidney injury could have caused transient oliguria, which could have led to reduced prednisone clearance, resulting in mania. His weight changed from 79.6 kg in the emergency room to 82.7 kg on day 5 with intravenous fluids; however, his glomerular filtration rate and creatinine trended back to baseline, so he likely continued to excrete urine. Although the general unit nursing measurement of fluid input and output showed he accumulated fluids, the measurements may be inaccurate because of lack of patient cooperation.

In addition, neurosyphilis can potentially present as manic symptoms,\(^5\) especially in an immunocompromised patient. Typical neurosyphilis CSF abnormalities are elevated protein concentration (typically less than 100 mg/dL), lymphocytic pleocytosis (typically less than 100 cells/\(\mu\)L), a reactive venereal disease research laboratory (VDRL) test, or a combination of the 3. Although our patient did have mild elevation in CSF protein of 63.3 mg/dL (reference range, 15–55 mg/dL), the remainder of his CSF laboratory test results were unremarkable, the MRI of his brain did not show significant atrophy, and there were no other neurologic manifestations of neurosyphilis.

In addition, illicit substances are known to cause mania, but our patient had a negative urine drug screen and urine test for synthetic cannabinoids. However, the presence of substances that are unable to be detected on standard urine drug screens cannot be ruled out.

Another differential could be bipolar II disorder because Mr. A may have had hypomanic episodes in his younger adult years that had gone undiagnosed, especially considering the prevalence of undiagnosed bipolar II disorder. Bipolar II symptoms are often ego syntonic and do not commonly lead to hospitalizations or impairment in functioning. Approximately 15% of patients with bipolar II disorder may eventually switch over to bipolar I.\(^7\) In this case, the added parameter of increased tacrolimus could have have triggered an underlying hypomanic episode that was not previously
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identified. However, bipolar II disorder is less likely in the differential owing to a negative family history and lack of a clear history of hypomania, mania, or depression. In addition, late-onset bipolar disorder is less likely, as only 5–10% of individuals with bipolar disorder are older than 50 years at the time of their first manic or hypomanic episode.10

Although the precise pathophysiology of mania is multifactorial and not well understood, inflammatory responses, glial cell dysfunction and neuro-inflammation, oxidative stress, and mitochondrial dysfunction have been hypothesized to play a role.10–13 The brain structures involved are less clear, and evidence shows that mania is likely caused by a dysfunction of interconnected brain networks. A detailed discussion of pathophysiological mechanisms of mania is beyond the scope of this study; we defer the reader to publications such as Maletic and Raison14 and Brady and Keshavan.15

The psychopathologic neurotoxicity resulting from tacrolimus medication is not fully understood, but several hypotheses have been put forward. One model suggests that the tacrolimus molecule, which is highly lipophilic, can cross the blood-brain barrier via enhanced nitrous oxide production, attach to myelin, and exert direct cytotoxic effects.5,16 Another suggested mechanism is that acute hypertension can lead to a loss of autoregulation, which in turn can lead to dilation of vessels and extravasation of protein and fluids (vasogenic edema) into the interstitium.16 One in vitro study of calcineurin inhibitor toxicity in mouse cortical neurons and glia showed that oligodendrocytes were more sensitive to the toxic effects than neurons.17

It should be noted that mania secondary to tacrolimus toxicity has manifested in patients with therapeutic tacrolimus levels, so the chance that tacrolimus may lead to hypomania or mania, despite being within the therapeutic range, cannot be ruled out. However these cases have been in patients with preexisting bipolar disorder, and although tacrolimus levels were within the normal range, they were found to be higher than the baseline range typical for the individual patients.18,19

Clinicians should be aware of mania as a possible manifestation of supratherapeutic tacrolimus toxicity, even in patients with no psychiatric history. Serum tacrolimus levels may not reflect continued presence of symptoms or severity once a patient is manic, and symptoms may persist even after the discontinuation of tacrolimus. While the pathophysiology of mania due to tacrolimus toxicity may be unique, the treatment options are the same as with any other presentation of mania, which includes mood stabilizers and/or antipsychotics. Rapid discontinuation of psychotropic medications is ill-advised, and we cannot comment on the recommended duration of treatment for this presentation of mania. More case reports of mania correlated with supratherapeutic tacrolimus will help guide clinical decision making about choice and duration of pharmacotherapy and will assist with creating guidelines for deciding on the possible continuation of tacrolimus once symptoms are resolved. Furthermore, this case demonstrates a complicated patient requiring collaborative effort between multiple specialties for appropriately managing care.

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