Tacrolimus-Induced Akathisia in a Post-Cardiac Transplant Patient: A Case Report

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Abstract

Akathisia, a prevalent drug-induced movement disorder, is characterized by inner restlessness and an irresistible urge to move. It can occur after starting a new medication, increasing the dose, or switching to another medication. It is commonly associated with, but not limited to antipsychotic use. Tacrolimus (TAC), an immunosuppressant vital for preventing acute rejection post-solid organ transplantation, has been linked to various neurological side effects. Neurotoxic side effects of TAC may include headache, seizures, tremor, encephalopathy, and peripheral pain. This report details a case of tacrolimus-induced akathisia in a post-cardiac transplant patient, emphasizing the need for heightened clinical suspicion and awareness of this underreported phenomenon. The patient's symptoms, including restlessness and an inability to sit still, were exacerbated by TAC, prompting a diagnosis and subsequent treatment for akathisia.

Keywords: Akathisia, Drug-Induced; Immunosuppressive Agents; Psychomotor Agitation; Tacrolimus; Organ Transplantation.

Introduction

Drug-induced movement disorders encompass a spectrum of manifestations, with akathisia being a common yet frequently unrecognized condition.[1,2]Akathisia is defined as a condition that causes an inner feeling of restlessness and the urge to move.[2] It can occur after starting a new medication, increasing the dose, or switching to another medication.[1] Unlike some movement disorders, which can be presented with external signs such as tremors, patients with akathisia describe a subjective sense of inner restlessness that may manifest as pacing or an inability to sit still, inner tension, anxiety, panic, irritability, discomfort, and sleeplessness. In severe cases, the thought processes of affected patients may become disorganized and their judgment impaired.[1–3] Also, impulsive behavior and/or suicidal ideation may be seen. However, some external manifestations like repetitive, purposeful, stereotypical, or suppressible movement can also be seen in some patients. For example, crossing and uncrossing the legs, rubbing the scalp or interior thighs, and rocking while sitting.[2]

Currently, akathisia is a diagnosis made purely by clinical observation and patient report, as there is no confirmatory blood test, imaging assessment, or neurophysiological study available. The most commonly used tool for assessment is the Barnes Akathisia Rating Scale (BARS), which is a four-item scale in which the subjective and objective components of the condition are rated separately and then combined.[3]

The management of akathisia includes cautiously reducing the medication dosage or switching to a medication with less potential to cause extrapyramidal symptoms; adding a beta-blocker (e.g., propranolol), an anticholinergic (e.g., benztropine), or, less commonly, a benzodiazepine (e.g., lorazepam) may be required to mitigate the symptoms especially if discontinuation of the culprit drug is not an option.[3-6]

Tacrolimus (TAC) is an immunosuppressant belonging to the class of calcineurin inhibitors that has been proven to prevent acute rejection after solid organ transplantation. Despite having dramatically improved survival after solid organ transplantation, TAC is associated with a number of neurological side effects, which have been demonstrated to have a significant impact on patients' quality of life. Neurotoxicity secondary to TAC may be due to low levels of vasoconstrictive cerebellar or cerebral ischemia induced by the drug. Patients may present with different neurological and psychiatric manifestations. These symptoms can be mild such as tremors, neuralgia, and peripheral neuropathy, or severe such as psychoses, hallucinations, cortical blindness, seizures, cerebellar ataxia, and motor weakness.[7,8] Although akathisia is more common with antipsychotics, akathisia has also been reported with the antibiotic azithromycin, calcium channel blockers, lithium, and drugs often used for recreational purposes.[9–11] Interestingly, tacrolimus-induced akathisia was reported in 1992 in a post-renal transplant patient by Bernstein et al.[12] We here report a case of tacrolimus-induced akathisia in a post-cardiac transplant patient.

Case Report

A 64-year-old female with a history of heart transplant, diabetes mellitus type II, and hypothyroidism experienced progressively severe symptoms of restlessness and an urge to move after initiating tacrolimus therapy. The heart transplant was performed in September 2016 without immediate complications. She received tacrolimus (1 mg BID for three days, then gradually increased up to 5 mg BID and adjusting the dose according to FK 506.), mycophenolate mofetil (1500 mg OD), and prednisolone (5 mg OD). In April 2020, she started having trembling legs when standing and a swaying upper body that improved with walking. The symptoms did not bother her initially. Her symptoms were progressive until they became severe enough to interfere with her daily activities and she needed someone to be with her most of the time. In August 2022, she came to our clinic, where she was initially diagnosed with a functional disorder, as her physical examination, brain MRI, and nerve conduction study /EMG were normal, and there was no recent event or new medication. She described her symptoms as an inability to sit still with an urge to move. She also had intermittent postural tremors in the upper and lower limbs. She feels better when she is constantly moving, such as walking or fidgeting. She also suffered from chronic anxious thoughts that affected her sleep. She had no other neurological symptoms.

Examination showed a vitally stable woman with intact cognitive function and unremarkable cranial nerve examination. Motor examination showed power 5/5 with normal tone and reflexes. All sensory modalities were also intact and cerebellar examination was unremarkable. She had a normal gait but could not perform a tandem gait and had an impaired Romberg test.

Investigations were unremarkable except for a high level of methylmalonic acid with normal B12. Nerve conduction study and electromyography revealed no evidence of peripheral neuropathy. Brain MRI and magnetic resonance angiography (MRA)were unremarkable.

At her first visit, she was not given any medications. At the next visit, she was treated with propranolol 10 mg daily for a week and then increased to 20 mg daily. A month later, she came to the clinic complaining of palpitations and worsening symptoms, at which point the propranolol was discontinued. She is now being treated with clonazepam 0.5 OD, with an increase in dose being considered at the next visit. She has regular follow-up visits at the movement disorders clinic.

Discussion

TAC has been reported to cause neurotoxicity with different clinical manifestations. Tacrolimus-induced akathisia was reported in 1992 in a post-renal transplant case, and the patient improved to his baseline after receiving propranolol and haloperidol.[12] Our patient had a sense of restlessness, a feeling uncomfortable sitting still with the urge to move and felt better with continuous movements. Her symptoms and the temporal relationship with the onset of the new medication are typical of akathisia. In this patient, these symptoms began after starting TAC, and her symptoms were progressive and did not improve because we did not discontinue TAC and she could not tolerate propranolol. In addition, the possible causes and medications that could cause akathisia were reviewed

and not found in her case. The lack of response to propranolol and its intolerance in our patient could be related to the heart transplant. The previously reported case and our case share common things, including akathisia and anxiety symptoms, which developed after the surgery. A prospective, cross-sectional study of 25 renal transplant recipients has been done to determine whether akathisia occurred and/or had a relationship to TAC plasma levels. They used Akathisia Rating Scales (ARS) to detect drug-induced akathisia, and Hamilton Anxiety (HAM-A) was used to measure anxiety symptoms. The study showed that higher TAC plasma levels correlated with higher HAM-A scores. ARS scores did not correlate with TAC plasma levels. They concluded that higher TAC plasma levels are more associated with features of anxiety than akathisia.[13] Tacrolimus-induced akathisia, a case from 1992, occurred after renal transplantation, whereas in our patient it occurred after cardiac transplantation, which may suggest that tacrolimus-induced akathisia and anxiety may not be related to drug clearance after renal transplantation.

This case highlights the importance of maintaining a high clinical suspicion for akathisia and remembering this when a patient presents with acute onset with restlessness in the setting of post-transplant surgery and a new immunosuppressant started. Akathisia is a treatable condition with a good prognosis if the condition is recognized and the drug causing it is discontinued. However, if the condition is left untreated, it has high morbidity and can even lead to suicidal ideations.[14] Detecting the symptoms and initiating a treatment plan with the primary team will help the patient comply with treatment, trust treating physicians, and limit unnecessary investigations. Even though our patient's symptoms did not improve, mainly because she did not tolerate propranolol, and we could not change her management plan at that time. It is also important to ask specifically about anxiety and akathisia symptoms. Akathisia's clinical picture may mimic anxiety as they share common features, and the symptoms can overlap. For example, patients with anxiety can present with restlessness and insomnia. Asking about symptoms specifically will help track if the akathisia worsens or if the patient develops anxiety too. It will guide the management, as each has a different approach. Tacrolimus-induced akathisia has been reported only by Bernstein et al.,[12] and, to the best of our knowledge, ours is the second case.

TAC has significant clinical implications, given its growing popularity as an immunosuppressant. Knowing the fact that TAC may cause akathisia, it is important to review patient medications prior to starting TAC and try to avoid other medications that are reported to cause akathisia to prevent drug-drug interaction.[2]

Conclusion

Akathisia may be common but underreported or unrecognized. This report raises awareness of this possibility. It will help prevent such adverse effects and their negative consequences on treatment adherence and healthcare costs. It will add valuable data to the existing literature. Further studies are needed to investigate the relationship between TAC and akathisia.

Disclosure

The authors declared no conflicts of interest. Informed consent was obtained from the patient.

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