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Tonic-Clonic Seizure in a Liver-Transplant Recipient due to Concomitant Use of Colchicine with Cyclosporine A and Valganciclovir

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Case Report

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Abstract

Use of immunosuppressant was inevitable in post-transplant recipients for prevention and treatment of allograft rejection. Concomitant use of antivirals in prevention of *Cytomegalovirus* disease after transplantation were common; and reduction in acute allograft rejection and all-cause mortality had also been shown. However, adverse effects from potential interactions between immunosuppressants and antiviral would have been overlooked easily; especially when adverse effects were further potentiated by addition of other medications for trivial conditions. Colchicine was commonly prescribed for clinical gout that occurred at higher incidences in post-transplant recipients on cyclosporine A or tacrolimus. We reported a post-LT patient developed his first tonic-clonic seizure from concomitant use of colchicine with CSA and valganciclovir.

Keywords: Seizure; Colchicine; Cyclosporine A; Valganciclovir; Liver transplant

Abbreviations: CMV: Cytomegalovirus; LT: Liver Transplantation; CSA: Cyclosporine A; MMF: Mycophenolate Mofetil; SOT: Solid-Organ Transplant; CSF: Cerebrospinal Fluid.

Introduction

Use of immunosuppressant was inevitable in post-transplant recipients for prevention and treatment of allograft rejection. Concomitant use of immunosuppressant and antivirals was common in transplant recipients [1]. Prevention of *Cytomegalovirus* (CMV) disease after liver transplantation (LT) by either pre-emptive therapy or antiviral prophylaxis, including ganciclovir (intravenous or oral) or valganciclovir, had been shown to reduce CMV infection by 40% and CMV disease by 58-80% respectively, and a 25% reduction in acute allograft rejection and all-cause mortality [2, 3].

Hyperuricaemia and clinical gout had been noted in post-LT patients on cyclosporine A (CSA) or tacrolimus [4]. Up to 6% and 28% of post-LT and post-transplant patients respectively developed clinical gout that colchicine might be required [5, 6]. However, such drug combinations in post-transplant recipients were not without risk, in particular the adverse effects from potential drug-drug interactions. We reported a post-LT patient developed his first tonic-clonic seizure from concomitant use of colchicine with CSA and valganciclovir; and subsequent recurrence even on CSA and valganciclovir without colchicine.

Case

The patient was a 62-year-old man who was a recipient of living-donor liver transplantation for acute liver failure with right anterior sectionectomy done for hepatitis B virus (HBV)-related hepatocellular carcinoma. He also had history of hypertension. He did not receive any pre-LT conditioning therapy and post-LT anti-rejection therapy. He had completed immediate-post-LT 3-months antiviral CMV prophylaxis. His immunosuppressant post-LT included CSA and mycophenolate mofetil (MMF).

On day-158 post-LT, he was admitted with a 5-day history of productive cough, rhinorrhoea, malaise, low grade temperature and chills, abdominal pain and diarrhoea. His mental and hemodynamic status was stable. Chest auscultation and X-ray showed right lower zone coarse crepitations, and right lower zone haziness respectively. Initial investigations were performed (Table 1). Empirical antimicrobial therapy was started and treated as community-acquired pneumonia. CSA, as part of his usual immunosuppressant regimen was continued but MMF was stopped. His nasopharyngeal swab for viral culture was subsequently positive for *Parainfluenza virus* type 4 (Table 1).

Tests	Results	Reference range
Complete blood picture		
White blood cell (wcc, $x10^9$/L)	4.09	3.7-9.3
Neutrophil ($x10^9$/L)	3.71	1.8-6.2
Lymphocyte ($x\ 10^9$/L)	0.17	1.0-3.2
Monocyte ($x10^9$/L)	0.21	0.2-0.7
Hemoglobin (Hb, g/dL)	8.5	11.5-15.4
Platelet (Plt, $x10^9$/L)	127	8.1-11.5
Clotting profile		
PT (sec)	12	10.1-12.4
INR	1.1	
APTT (sec)	30.3	25.1 – 35.5
Renal function test		
Sodium (Na, mmol/L)	129	136-145
Potassium (K, mmol/L)	3.6	3.5-5.1
Urea (mmol/L)	18.2	<8.3
Creatinine (umol/L)	191	44-80
Liver function test		
Total protein (g/L)	54	64-83
Albumin (Alb, g/L)	23	35-52
Globulin (Glo, g/L)	31	24-37
Bilirubin, total (μmol/L)	5	<17
Alkaline phosphatase (ALP, U/L)	45	35-104
Alanine transaminase (ALT, U/L)	21	<33
Aspartate transaminase (AST, U/L)	28	<38
Nasopharyngeal aspirate		
Direct antigen detection by immunofluorescence	Negative for *Influenza A & B viruses*, *Parainfluenza viruses* 1,2 &3, *Respiratory Syncytial virus* and *Adenovirus*	
Viral culture	Positive for *Parainfluenza virus* 4	

Table 1: Results of initial laboratory investigation for the patient.

On day-3 post-admission, he developed acute gouty attack and treated with oral colchicine 0.5mg twice daily. On day-5 post-admission, he was found to have CMV pp65 antigenemia, oral valganciclovir 450mg at 48 hourly was prescribed. On day-7 post-admission, the CMVpp65 antigen in plasma decreased from 30 per $2x10^5$ white blood cells (wbc) to 8 per $2x10^5$ wbc after 2-day valganciclovir use. After concomitant use of CSA, valganciclovir, and colchicine, he developed the first episode of tonic-clonic convulsion lasting < 1 minute for 3 times, each of which was spontaneously aborted and subsequently controlled by phenytoin. CSA, valganciclovir, and colchicine were stopped immediately. Other medications including entecavir and ticarcillin-clavunate were continued (Table 2). Laboratory investigations were unremarkable with slightly improved urea and creatinine levels at 13 and 129mmol/L respectively, normal glucose

4.3mmol/L and ammonia <9umol/L. The magnetic resonance imaging of the brain showed cerebral microangiopathic and atrophic changes without features suggestive of encephalitis. Lumbar puncture was performed and the cerebrospinal fluid (CSF) analysis and microbiological investigations were unremarkable (Table 3).

Cerebrospinal fluid (CSF) (reference range)	Result
Colour	Colorless
Turbidity	Clear
Total cell count	0
Erythrocyte (absent)	Absent
Protein (0.12-0.60 g/L)	0.28
Glucose (2.2-3.9 mmol/L)	3.9
Cryptococcal antigen (negative)	Negative
Smear	
Gram stain	Negative
Acid-fast bacilli (AFB)	Negative
Fungus	Negative
Culture	
Bacteria	No growth
AFB	No growth
Fungus	No growth
PCR	
Herpes simplex virus	Negative
Varicella-zoster virus	Negative
Enterovirus	Negative
JC virus	Negative
Mycobacterium tuberculosis complex	Negative
Blood	
Glucose (2hr pp <7.8 mmol/L)	5.6
Bacterial culture	No growth
Mid-stream urine	
Bacterial culture	No growth

Table 3: Results of biochemical and microbiological investigations performed for the first seizure of our patient.

He developed another episode of tonic-clonic convulsion at 5-days after reintroduction of CSA and valganciclovir even on phenytoin, without concomitant use of colchicine. Both CSA and valganciclovir were then stopped immediately. The serum CSA drug level profile had been within reference range all-along. CSA was subsequently reintroduced alone, and no seizure for ≥ 6 months during CSA monotherapy as immunosuppressant, and remained seizure-free on subsequent concomitant use of sirolimus and prednisolone.

Discussion

Seizure was the second most common neurologic complications post-LT [7, 8], with reported incidence varied from 15% to 40% [7-9], and a higher incidence up to 33% in re-LT recipients [9]. Our patient's seizure developed at ~22 weeks post-LT, which was later than the typically described period: >2/3 developed in the initial 4 weeks early post-LT or in bimodal distribution that >50% occurred in the initial week, and then 5 to 16 weeks post-LT [7-9]. Concordant with previous reports, tonic-clonic seizure was the commonest form of seizure in post-LT recipients [7-9]. About 9% to 12% of seizures in post-LT recipients were status epilepticus [7, 9]. The cause of seizure could be multifactorial. Causes such as electrolyte and metabolic disturbances, central nervous system infection and structural abnormalities, hypoxic-ischaemic encephalopathy, cerebrovascular complications [7-10] had been excluded in our patient.

Parainfluenza virus type 4 was isolated from our patient's nasopharyngeal aspirate. However, his clinical, CSF and radiological findings were not suggestive of viral encephalitis and/or post-infectious encephalitis; the latter was considered as immune-mediated usually occur at 2 to 30 days after initial infection [11].

Our patient's seizure was unlikely solely due to CSA, as part of CSA acute encephalopathy and seizure syndrome, or CSA neurotoxicity. The latter would also present with tremors, altered conscious state and encephalopathy, which occurred at 1% to 10% or relatively higher in solid-organ transplant (SOT) patients; and mediated through inhibition of γ-aminobutyric acid (GABA)-ergic transmission and activation of serotoninergic neural activities [12-14]. Our patient had been seizure-free all-along on CSA, either in combination with MMF before admission, or subsequent monotherapy after his last seizure episode, or later concomitantly with sirolimus and prednisolone. Moreover, he did not experience any common side effects of CSA, such as exaggerated blood pressure on his underlying hypertension, gingival hyperplasia, hirsutism, and mild-to-moderate hyperbilirubinemia [15]. Nevertheless, our patient's serum CSA levels were concordant with previous findings that serum trough CSA levels were found within reference range in seizures of post-LT patients, despite neurotoxicity usually occur when higher doses were used

[10]. Mice model with partial hepatectomy in simulation to transient liver dysfunction at early phase post-LT was shown to increase susceptibility of CSA-induced neurotoxicity mediated by reduced blood-brain barrier function [13]. This might explain seizure occurrence in early weeks post-LT. CSA, a calcineurin inhibitor, had been widely used to prevent allograft rejection in SOT patients and to treat various autoimmune diseases by inhibit the production and release of interleukin-2 (IL-2), and the IL-2-induced activation of resting T-lymphocytes [12].

Concomitant use of CSA with colchicine increased the colchicine maximum observed plasma concentration which might potentiate colchicine gastrointestinal side effects, dose-related myelosuppression, and other toxicities such as renal and liver impairment, polyneuropathy, myopathy, rhabdomyolysis and cardiovascular effects such as heart failure and ventricular arrhythmia [15,16]. Nevertheless, these were not evident in our patient. CSA had been shown to inhibit colchicine excretion via kidney and liver in animal model [15]. Moreover, CSA also inhibit colchicine efflux from nerve and muscle cells resulted in neurotoxicity and myotoxicity especially in renal and liver impaired patients [16].

The mechanism was due to potent inhibitory effect of CSA on P-glycoprotein drug transport system [16]. It was suggested that either a 50% reduced colchicine dose was used whenever with CSA was concomitantly indicated, or a switch of CSA to other immunosuppressants; and similar was applicable to tacrolimus [16]. Other immunosuppressant such as FK506 and OKT3 also predisposed to seizure development [10]. Our patient received colchicine at 0.5mg twice daily, which seems to be higher than the studied dose of 0.6mg daily and the suggested reduced dose at 0.3mg daily orally [16]. On the other hand, colchicine had been reported as a convulsant agent in animal models [17,18]. Colchicine, which was a tubulin depolymerizing agents, its neurotoxicity had been shown related to destruction of microtubules of selected neural cells leading to accumulation of metabolic toxic cellular products [17]. Colchicine was shown to induce hippocampal granule cells hyperexcitability with inter-ictal epileptic spike or electrographic seizures [18]. Colchicine was shown to be competitive antagonist at human recombinant γ-GABA(A) receptor, either through direct interaction at receptor binding site or receptor affinity modulation by allosteric interaction with other binding site or receptor associated protein; and CSA was shown to enhance colchicine induced apoptosis in cerebellar granule neurons of rats [19]. Concomitantly, CSA absorption was increased by concomitant use of colchicine, hence the CSA drug level in blood [12]. Transplant or autoimmune-diseased patients on CSA were found to have a higher incidence of hyperuricemia and clinically gouty attack [16,20]. When colchicine was prescribed for the latter, this might initiate drug interactions for complications.

An apparent temporal relationship to the concomitant introduction of CSA and valganciclovir, with and without colchicine, was observed for the seizure recurrence in our patient. Drug interactions between immunosuppressant and antiviral with tonic-clonic convulsion in patients with recurrent herpetic keratitis [11], transient neutropenia and its association of trough MMF level with valganciclovir in renal-transplant patients [16], had been suggested previously for MMF but not for CSA. MMF in our patient had been stopped before his first seizure developed, despite its metabolite mycophenolic glucuronide would raise the intracellular concentration of acyclovir or valganciclovir to haematotoxic levels by competing for renal tubular secretion, resulted in exacerbation of neurotoxicity and cytopenic side effects of acyclovir [21,22] However, valganciclovir had been shown causing additive nephrotoxicity with CSA [23]. Valganciclovir had been widely used for prevention of CMV infection in high-risk SOT recipients, with good tolerability except the higher incidences of neutropenia that usually developed after prolonged use for 3 months, and nephrotoxicity [2,24,25]. Tonic-clonic convulsion was rarely occurred at <5% as side effect of valganciclovir [26]. The neurotoxicity of valganciclovir was reported in <1% of adult post-LT patients on low dose as prophylaxis; and manifested as mental confusion and hallucination in a child post-haemopoietic stem cell transplant without concomitant CSA use [27,28].

Cyclosporine A
Valganciclovir
Colchicine
Entecavir
Ticarcillin-clavunate
Fluconazole
Metoprolol
Amlodipine
Esomeprazole
Ursodeoxycholic acid

Table 2: List of medications the patient was taken when the first seizure developed.

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In summary, we reported a rarely occurred complication from a commonly used drug combination regimen, which not only for post-LT, but also other post-transplant patients in clinical practice. Vigilant awareness from clinicians and transplant expertise were important to note such potentially fatal complication or with significant morbidity from drug combination and interaction. Further researches were needed for underlying mechanisms of the drug interaction, so as to guide further for clinical recommendations accordingly.

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