Reversible Calcineurin Inhibitor-associated Sensorimotor Polyneuropathy in a Lung Transplant Recipient: A Case Report

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ABSTRACT

Calcineurin inhibitors (CNIs) are regarded as a corner stone in immunosuppressive therapy after solid organ transplantation. However, neurotoxicity is a common side effect of CNIs, resulting in a wide range of neurological symptoms such as headache, tremor and seizures. In this case report, we describe a patient who developed severe motor and sensory neuron dysfunction related to CNIs after bilateral lung transplantation, which resolved after halting CNI and switching to a mammalian Target of Rapamycin-inhibitor.

KEYWORDS: Calcineurin inhibitors; mTOR-inhibitor; Lung transplantation; Reversible neuropathy

INTRODUCTION

After the introduction and improvement of immunosuppressive therapy, allograft survival rates have increased significantly. A drawback of this success is a strong increase in the prevalence of side-effects such as neuropathy, occurring in up to 85% of transplant recipients [1].

CNIs are the leading cause of drug related neurotoxicity in transplant recipients [1]. By inhibiting calcineurin, the release of interleukin 2 and proliferation of T-cells is suppressed, preventing allograft rejection (Fig 1a). However, inhibiting calcineurin also suppresses the regulation of neuronal function and excitability, potentially triggering neuropathy [2].

New onset diabetes after transplantation (NODAT) is a well-known complication after initiation of immunosuppressive therapy which can cause neuropathy in transplant recipients [3]. Other causes of peripheral neuropathy like opportunistic infections, vascular complications, perioperative nerve injury and systemic diseases should also be excluded [4].

In this case report, we discuss a lung transplant recipient who developed neuropathy after transplantation, which recuperated after changing immunosuppressive therapy.

Neuropathy after SOT has frequently been described, but not much is known about the reversibility of neuropathy after transplantation and the incidence and mechanisms of this reversibility [1].

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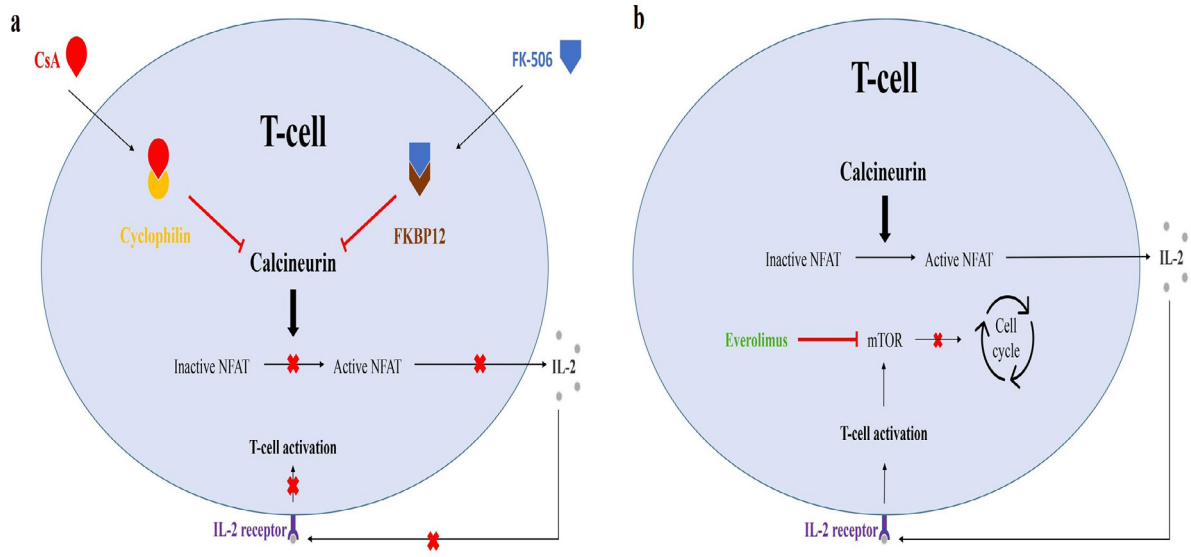

Figure 1: (**a**) **Working mechanism of calcineurin inhibitors CsA (cyclosporin) and tacrolimus.** CsA inhibits calcineurin by binding to the immunophilin cyclophilin. Tacrolimus inhibits calcineurin by binding to the intracellular protein FKBP-12. Each of these complexes inhibit the phosphatase activity of calcineurin. This prevents the dephosphorylation and activation of NFAT, a nuclear component that initiates gene transcription for the formation of IL-2. IL-2 is a critical growth factor for T-cell proliferation,
(**b**) **Working mechanism of mTOR inhibitor everolimus.** Everolimus works by inhibiting the mammalian target of rapamycin, a protein kinase that regulates cellular metabolism, growth and proliferation. mTOR stimulates the cell cycle, causing T-cells to replicate. Inhibiting mTOR prevents replication of T-cells

CASE PRESENTATION

A 63-year old female with chronic kidney disease received a bilateral lung transplant in August 2016 due to non-cystic fibrosis bronchiectasis. She was put on an immunosuppressive regimen consisting of cyclosporine (CsA), mycophenolate mofetil (MMF) and corticosteroids. Due to a mild acute graft rejection three months after transplant, CsA was discontinued and replaced by tacrolimus (Fig 2).

The first symptoms of neuropathy started seven months after transplantation and involved sensory loss in the patient's hands and feet. The patient did not suffer from DM or NODAT so these were ruled out as causes of neuropathy. Other possible causes were evaluated by frequent laboratory and clinical testing. Vitamin B12 remained within the normal range throughout the whole period of follow up, with the lowest value being 430 ng/mL. Serum and urine electrophoresis, erythrocyte sedimentation rate and thyroid function testing showed normal values, thus excluding these as possible sources of the neuropathy. Indirect immunofluorescence two months before transplantation showed the presence of positive antinuclear cytoplasmatic antibodies for IgG. Antinuclear antibodies were negative.

Upcoming neuropathic pain was treated with pregabalin 75 mg twice daily and paracetamol 1g 4 times a day as needed while cortical functions remained intact. The neuropathy worsened over time with progressive hyposensibility of both feet, decreased reflexes (achilles tendon reflex 0/4) and reduced force of the lower left leg (motor strength 4/5). EMG revealed severe axonal sensorimotor polyneuropathy with signs of denervation in the left musculus rectus femoris and musculus tibialis anterior. Furthermore, there was a mild decrease in sense of vibration (5" at the ankles, 6" at the knees and > 20" at the wrists) and a mild reduced sensation to pinprick and joint position in the left leg. The decline in sensorimotor functioning had a great impact on the

Figure 2: Visual evolution of walking ability patient according to time after lung transplantation. Three months after transplantation (A.T.): Normal recuperation.
4 months A.T.: Switch to tacrolimus due to mild acute allograft rejection.
7 months A.T.: Development of progressive neuropathy after switch to tacrolimus.
14 months A.T.: Switch to CsA. No improvement progressive neuropathy and disability leads to use of wheelchair.
18 months A.T.: Switch to mTOR inhibitor leads to improvement in neuropathy and an almost complete reversibility of disability.
27 months A.T.: Switch to tacrolimus during pre- and postoperative period leads to development of neuropathy.
31 months A.T.: Switch to mTOR inhibitor leads to improvement in neuropathy.
CsA, cyclosporin; tacrolimus; mTOR inhibitor, mammalian Target of Rapamycin inhibitor

mobility of the patient. The upper extremities showed no deficits.

Despite metabolic optimization, vitamin B supplementation, corticosteroid reduction and switch from tacrolimus back to cyclosporine, the neuropathy remained progressive. Eighteen months after transplant the patient was severely disabled, needing a walker and a wheelchair. Therefore, treatment with CNI (cyclosporine) was halted and replaced by the mTOR inhibitor everolimus. This finally resulted in a stabilization of the neuropathy with improvement of functioning over the next year. Later, the patient developed a cholecystitis and was indicated for a cholecystectomy. To diminish surgical complications caused by the mTOR inhibitor, everolimus was stopped and again switched to tacrolimus.

During treatment with tacrolimus the patient developed the same neuropathy which disappeared again after switching to mTOR inhibitor. Moreover, we noted an important clinical improvement and recovery of functionality (Fig 3).

Four years after the bilateral lung transplantation the patient is doing well. There are no signs of chronic allograft rejection. Despite a persisting left-sided drop foot, the patient can walk autonomously without any support. EMG shows a positive evolution in strength. The neuropathic pain has improved with only a sporadic need for pregabalin therapy. Her chronic kidney disease (eGFR= 45-50 ml/min/1.73 m^2) has also improved from 47 to 57 ml/min/1.73 m^2.

DISCUSSION

The neuropathy, developed during treatment with CNI, improved when our patient switched to treatment with a mTOR inhibitor. Because of planned surgery, the patient was briefly switched back to CNI treatment, which led to the prompt reappearance of the signs and symptoms of neuropathy. After surgery, the mTOR inhibitor treatment was reinstalled, resulting yet again in a decrease of neurological symptoms.

Because of the temporal sequence of this reaction there is, according to the Naranjo Adverse Drug Reaction Probability Scale, a high probability that the CNI caused the severe sensorimotor complications in our patient. Neurotoxicity is a recognized side effect of CNI treatment. In both episodes, withdrawal of CNI caused significant improvement of symptoms. Other possible etiologies of axonal neuropathy such as reduced thyroid function,

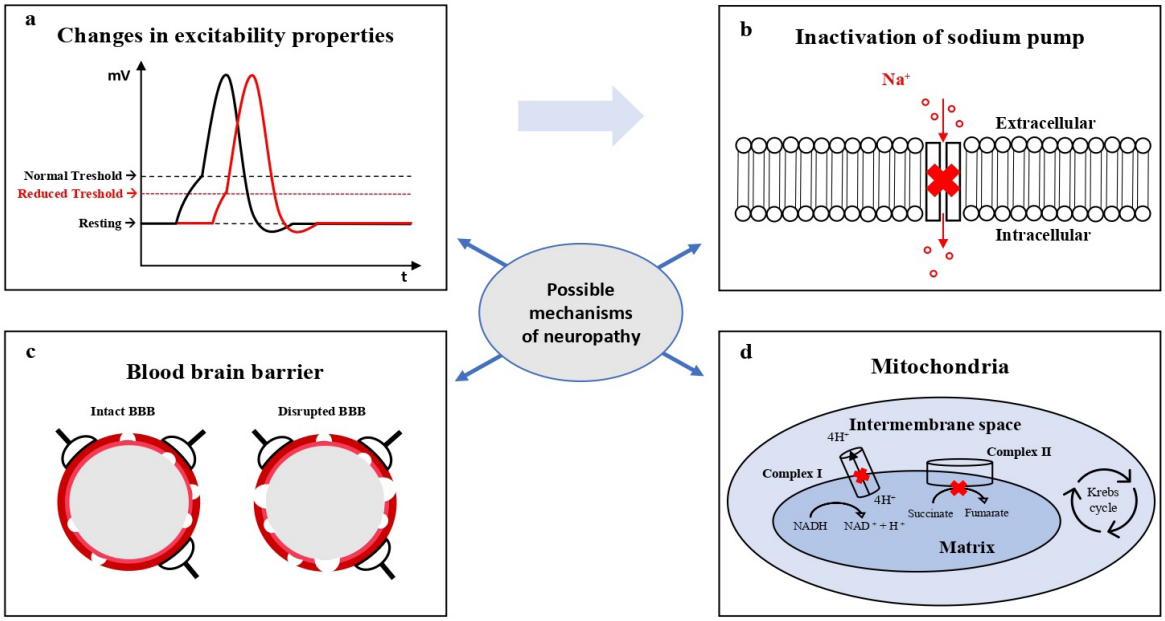

Figure 3: Possible mechanisms of neuropathy. (**a**) The use of CNIs may reduce the threshold for action potential generation and facilitate the development of neuropathic symptoms, including paraesthesia and cramps; (**b**) Severe nerve membrane depolarization can inactivate sodium channels, reducing the action potentials generated and causing neuropathic symptoms; (**c**) An intact BBB prevents non-selective crossing of solutes in the circulating blood into the cerebrospinal fluid of the CNS. A disrupted BBB allows passage of larger and lipophilic molecules such as CNIs, causing accumulation of CNI in the CNS and leading to neurotoxicity; (**d**) CNIs compromise the functioning of respiratory chain complex I and complex II, resulting in a decreased mitochondrial function and leading to neurotoxicity.

diabetic neuropathy, deficiencies in vitamin B12, raised erythrocyte sedimentation rate or changes in serum and urine electrophoresis were excluded. To our knowledge, this is the first report of largely reversible neuropathy in a lung transplant patient.

mTOR inhibitors act at a later stage in the cell cycle than CNIs (Fig 1b) [5]. They first bind to the cytosolic immunophilin FK-binding protein 12 (FKBP12), which then binds and subsequently inhibits the activation of mTOR, a key regulatory kinase, which causes suppression of cytokine-mediated T-cell proliferation [6]. mTOR inhibitors are being used to allow CNI-minimization and to avoid CNI-associated nephrotoxicity [6].

mTOR plays a key role in neuronal physiology and when its signalling is altered, it can lead to neuronal disorders such as tuberous sclerosis complex, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson and epilepsy [7]. Inhibiting mTOR activity is being studied as a new approach to an effective treatment of the disorders mentioned above and other neurodegenerative disorders. The neuroprotective properties of the mTOR-inhibitor might have led to an improvement in our patient's neuropathy. However, the effects of mTOR inhibition on the in vivo brain physiology is still largely unknown [8].

There are several mechanisms as to how CNIs cause neuropathy (Fig 3a-d). CNI treatment may affect neurovascular supply by causing endothelial dysfunction, leading to changes in excitability properties of nerve membranes and their depolarization [9].

Furthermore, nerve depolarization can facilitate the development of neuropathic symptoms by reducing the threshold for action potentials (Fig 3a). Severe nerve membrane depolarization can inactivate the sodium channels, reducing the action potentials generated and causing sensory loss and weakness (Fig 3b)

[9].

Joannides et al. showed that CNI-associated membrane depolarization improved when CNI was replaced by sirolimus (mTOR inhibitor), which is in line with the improvement seen in our patient's neuropathy [10]. Another case report by the group of Labate discusses a tacrolimus-induced polyneuropathy after heart transplantation, that was believed to be caused by direct tacrolimus neurotoxicity and was resolved by ending treatment with tacrolimus and switching to CsA [11]. This suggests that even between CNIs, there can be a varying presentation of side effect between patients.

Lastly, CNIs might also cause neuropathy by increasing the permeability of the blood brain barrier (BBB) and by altering mitochondrial function (Fig 3c-d) [12]. CNIs cause loss of junctions with neighbouring brain capillary endothelial cells and detachment of these cells from their substratum, impairing the BBB function and leading to accumulation of drugs in the brain. CNIs affect the functioning of respiratory chain-complexes and citrate synthase, causing altered mitochondrial function and aiding to the development of neurotoxicity [12].

The physiological mechanism of why and how the neuropathy was partially reversible, is yet unclear. The reversibility could solely be due to the discontinuation of the CNI but could also be due to an effect of the mTOR inhibitor. A combined effect of both actions is a plausible alternative.

Neuropathy is a common side effect of CNI treatment after solid organ transplant. To our knowledge, this is the first report describing an invalidating neuropathy in a lung transplant recipient which showed an almost full recovery after switching CNI to a mTOR inhibitor. Although the exact mechanism is not clarified yet, we speculate that CNIs affect the neurovascular supply and subsequently cause endothelial dysfunction, leading to changes in excitability properties of nerve membranes and their depolarization.

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CONFLICTS OF INTEREST: None declared.

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