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Case Report

Multiple Adverse Drug Reactions to Calcineurin Inhibitors in a Renal Transplant Patient

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Abstract: Calcineurin inhibitors (CNIs) are typically used to prevent organ rejection and their use has significantly improved allograft and survival rates with a marked reduction in rejection rates. However, CNIs have been associated with various side effects including nephrotoxicity, hypertension, gingival hyperplasia, hypertrichosis, hepatotoxicity, hyperkalemia, and neurotoxicity. Significant intra-patient and interpatient pharmacokinetic variability and narrow therapeutic indices make the therapy complicated. Although CNIs are essential in preventing organ rejection, higher doses could lead to toxicity, which can reduce patient tolerability and negatively affect long-term allograft survival and patient mortality. As individual patients respond differently to comparable drug levels, attaining the optimal drug level range does not ensure lack of drug toxicity or complete immunosuppressant viability. One to two adverse effects are commonly observed in patients using CNIs. However, no case about CNI-induced gingival hyperplasia, hypertrichosis, tremors, facial nerve palsy, and blepharospasm after kidney transplantation in a single patient has been reported. Our report describes the unusual case of a patient presenting with CNI-induced multiple adverse reactions.

Keywords: renal transplantation; calcineurin inhibitors; gingival hyperplasia; facial palsy; hypertrichosis

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1. Introduction

The use of the calcineurin inhibitors (CNIs), cyclosporine (cyclosporine A, CsA) and tacrolimus (TAC) in immunosuppressive therapy protocols has resulted in a significant breakthrough in transplant medicine and initiated a new era in transplantology with phenomenal short-term graft and patient survival [1,2]. CNIs are potent immunosuppressive agents, which have been the mainstay of immunosuppression in solid organ transplantation for almost five decades. Although CNIs are typically used for prevention of organ rejection, they are also used off-label in the management of certain autoimmune conditions such as rheumatoid arthritis, multiple sclerosis, psoriasis, systemic lupus erythematosus, and refractory nephrotic syndrome [3,4].

CsA is a cyclic endecapeptide [5], while TAC is a macrocyclic lactone [6]. They both have similar mechanisms of action, such as inhibition of calcineurin, which is a protein phosphatase [7]. The potential adverse events associated with TAC and CsA use are nephrotoxicity, hypertension, gingival hyperplasia (GH), hypertrichosis, hyperkalemia, neurotoxicity, hyperglycemia, infections, malignancy, and gastrointestinal disturbances including hepatotoxicity [4]. Although the two drugs have similar side effect profiles, they may vary in the frequency of adverse effects. For example, TAC is more likely to cause alopecia, tremors, and new-onset diabetes mellitus, whereas CsA is associated with hypolipoproteinemia, hypertrichosis, and GH [4,8–10]. Although CNIs are essential in preventing organ rejection, higher doses can lead to toxicity, which can reduce patient

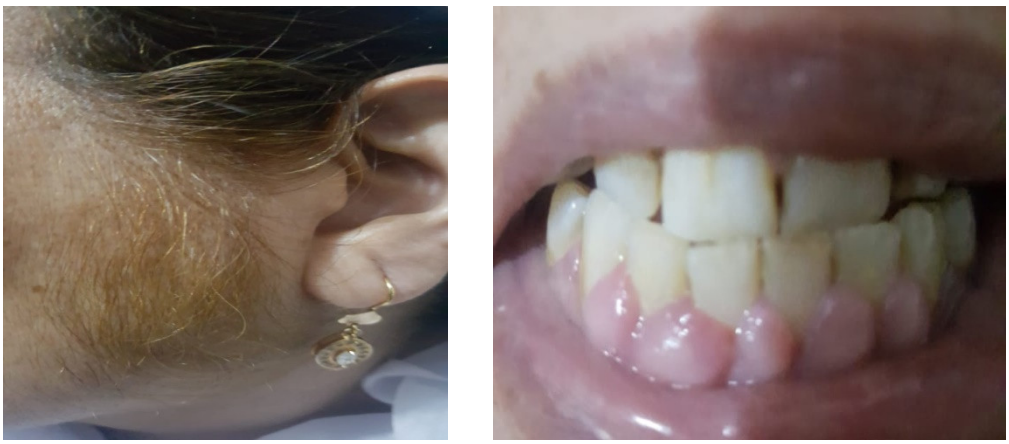
tolerability and negatively affect long-term allograft survival and patient mortality [4]. Therapeutic drug monitoring, therefore, is needed for both drugs.One to two adverse effects are commonly observed in patients using CNIs [11]. However, no case about CNI-induced gingival hyperplasia, hypertrichosis, tremors, facial nerve palsy, and blepharospasm after kidney transplantation in a single patient has been reported. Our report describes the unusual case of a patient presenting with CNI-induced multiple adverse reactions.

2. Case Presentation

A 38-year-old female, with end-stage renal disease due to hypertension, underwent living unrelated renal transplantation in 2011. She received hemodialysis for two months prior to her transplant, and her pre-transplant evaluation revealed a perfect match. Basiliximab (on day 1 and day 4) was given as induction immunosuppression.

She had an uneventful post-operative recovery with good allograft function and rapid normalization of serum creatinine to 1.0 mg/dL on the sixth day. Her discharge medications were CsA (5 mg/kg/day), mycophenolate mofetil (1 mg BID), methyl prednisolone10mg/day, trimethoprim–sulfamethoxazole prophylaxis, carvedilol, and amlodipine. The dose of CsA was adjusted according to the trough drug levels (targeted plasma level kept between 150 and 200 ng/mL).

There was no documented history of acute or chronic rejection. However, in February 2018, she presented to the outpatient department (OPD) with gum enlargement and increased hair growth. No additional details were available with regard to when these adverse drug reactions (ADRs) began to appear. Her physical examination was unremarkable except for hair growth all over the body, including the face (hypertrichosis), as shown in Figure 1a.On examining her oral cavity, she had enlarged gums with no signs of bleeding and fair oral hygiene, as shown in Figure 1b. There was a 7-year gap between hospital discharge after the renal transplant and her presentation in the OPD with ADRs (between 2011 and 2018). As CsA toxicity was suspected, the next dose of CsA was withheld and a serum CsA level was requested along with other routine laboratory investigations. Her blood count and chemistry were within a normal range. The CsA level was 694 ng/mL, and although this was well above the therapeutic range of 100–250 ng/mL, the patient had no other signs and symptoms of CsA toxicity.



(**a**) (**b**)

Figure 1. Two prominent ADRs in subject of case report: (**a**) CsA-induced hypertrichosis with thick facial hairs; (**b**) CsA-induced gingival hyperplasia.

The adverse drug reaction (ADR) score to CsA was eight after assessment on the probability scale using the Naranjo algorithm [12]. Because of this, CsA was discontinued, and TAC was initiated at 3 mg BID during her clinic visit, and then the patient was sent home. A few months later, she re-presented to the OPD with severe neurological symptoms that included tremors and continuous twitching movements of her left eye. She also

reported a deviation of the angle of her mouth with dribbling of saliva and difficulty in drinking liquids. She was found to be haemodynamically stable, and with a normal core body temperature.

Her neurological examination revealed normal forehead wrinkling with the patient's ability to elevate the right eyebrow intact. However, she had an obvious right-sided facial droop at rest with loss of her right nasolabial fold. She also had an asymmetrical smile on examination, as can be seen in Figure 2. An external ear examination did not reveal any vesicular rash, scabbing, erythema, or discharge. There was no taste disturbance or hyperacusis. The rest of her neurological and systemic assessment was unremarkable.

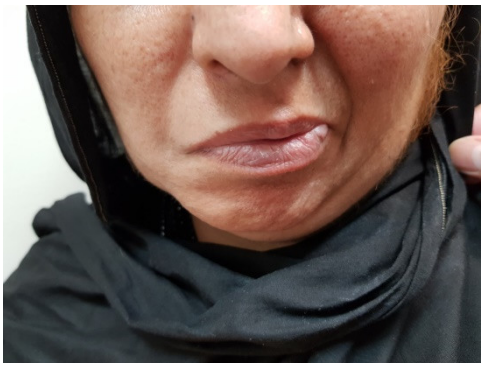


Figure 2. Facial nerve palsy induced by TAC. Drooping at the right corner of mouth and loss of right nasolabial fold are shown. The patient had only lower facial nerve involvement and upper face features were normal.

Her blood tests revealed a white blood cell count of 7.17 $\times$ 10^3 cells/µL, hemoglobin 11.2 mg/dL, and platelet count 213 $\times$ 10^3/µL. The HbA1c was elevated at 6.39% (4.8–6.4%) and a random blood glucose was 133 mg/dL. Other laboratory results were urea 22 mg/dL, creatinine 0.81 mg/dL, uric acid 5.3 mg/dL, tacrolimus trough level 15 ng/mL (target 5–20 ng/dL), calcium 9.2 mg/dL, phosphorus 4.3 mg/dL, sodium 138 mmol/L, potassium 4.41 mmol/L, albumin 3.8 g/dL, triglyceride 240 mg/dL, low-density lipoprotein 150 mg/dL, ALT40 U/L, and parathyroid hormone 80.5 pg/mL. Routine urinalysis was unremarkable. Her score was 4 on a Naranjo nomogram [12] for ADRs induced by tacrolimus. The patient was educated about the association of these side effects with TAC. However, she agreed to continue with the current regimen of immunosuppression in preference to CsA due to previous cosmetic concerns. The dose of TAC was reduced to 2 mg BID from 3 mg BID. She was referred to physiotherapy for her facial weakness, and follow-up was arranged on a thrice monthly basis. However, she was lost to follow up.

3. Discussion

With the discovery of CsA and TAC, transplant medicine transformed and CNIs are well established agents in human kidney, heart, liver, and lung transplants [1,4]. Although the benefits of CNIs are obvious, their use has been questioned due to various side effects which include GH (epithelial and sub-epithelial components to varying degrees), hirsutism, fine tremors, impaired renal function, hepatic dysfunction, gastrointestinal disorders, hypertension, and in rare instances, hair loss [9,10,13].

3.1. Gingival Hyperplasia (GH)

GH occurs in about 30% of patients treated with cyclosporine, with a prevalence ranging from 25 to 81%.This ADR typically manifests within six months of treatment, but our patient presented with GH almost seven years after starting CsA [13,14].The prevalence rate could be related to other risk factors influencing the development of this condition such as age, gender, genetic predisposition, oral cavity hygiene status, pharmacokinetic variables, immunological changes, and concomitant use of other medications such as

calcium channel blockers (CCBs) and gingival inflammation [11,13,15]. CsA-induced GH has an age and gender predilection, with children and males having a higher risk as compared with females and adults [13,16].

Apart from aesthetic concerns, CsA-induced GH can implicitly limit functional ability, hence, compromising nutrition and oral hygiene [13]. Our patient experienced this due to continuous dribbling of saliva and difficulty in drinking liquids. On examining her oral cavity, she had enlarged gums with no signs of bleeding and fair oral hygiene. The precise mechanism of CsA-induced GH is unknown, but the cause is likely multifactorial, such as upregulationor overexpression of salivary inflammatory cytokines, including interleukin (IL-1α), IL-6, and IL-8; increased proliferation of gingival fibrous connective tissue and keratinocytes; and inhibition of gingival cell death [11].

Oral health, dose and length of CsA treatment, serum level of CsA, simultaneous use of other medications with CsA, age, and concomitant conditions likewise modify the incidence and severity of the gingival overgrowth [11,13,15]. In our case, the patient's oral hygiene was satisfactory. However, the serum CsA level was quite high at 649 ng/mL (therapeutic range 100–250 ng/mL). She was also taking 10mg of amlodipine once daily, along with the CsA. The high level of CsA could also be attributed to a drug interaction between amlodipine and CsA, as serum levels of CsA increase when both drugs are used concomitantly.

Among the most important group of drugs that cause GH are calcium channel blockers, such as nifedipine and amlodipine. The prevalence of GH with the concomitant use of CsA and nifedipine is between 48 and 60%. However, with the use of CsA and amlodipine, the frequency of this ADR is lower at 1.7–3.3% [13,14]. Ellis et al. were the first to report amlodipine-induced GH (AIGH) in patients taking calcium channel blockers [17]. Presently, there are many published reports of nifedipine-induced gingival overgrowth, but limited reports on AIGH. Although the literature supports the view that GH is more common amongst patients who take nifedipine as compared with those treated with amlodipine, a study by James et al. in renal transplant recipients on CsA and either amlodipine or nifedipine showed a higher prevalence of GH in the amlodipine group (72%) as compared with the nifedipine group (53%) [18]. Nifedipine and amlodipine differ in their physicochemical profile and concentrations obtained in gingival crevicular fluid (GCF) [19]. The mean nifedipine levels were 84 times higher when comparing concentrations in GCF vs serum in seven patients reported by Ellis et al. in 1992 [15]. In comparison, the mean amlodipine levels were 176 times higher in GCF vs. plasma in three patients studied by Ellis et al., in 1993 [15].

3.2. Hypertrichosis

Hypertrichosis is a common adverse effect associated with CsA, with an incidence of 95% in one report. Increased hair growth appears within a few months after the start of therapy with CsA and unless the dose is reduced it remains constant. However, the peer-reviewed literature has not established a relationship between hypertrichosis and serum CsA levels [20]. Hypertrichosis is an unwanted, worrisome cosmetic problem particularly for females, as seen in our patient who complained of increased hair growth over her entire body, including the face. In her case, it was associated with a high CsA level. As CsA toxicity was the suspected cause, the next dose of CsA was withheld and a serum CsA level and other routine laboratory investigations were obtained. Because of the high trough level of 694 ng/mL, CsA was stopped and tacrolimus (TAC) at 3 mg BID was started. Tacrolimus has been marketed as an effective alternative immunosuppressant to CsA that does not result in side effects such as hypertrichosis and GH, and has a minimal risk of rejection or allograft dysfunction [1,4].

3.3. Neurotoxicity

A few months later, our patient presented to the OPD with severe neurological complications characterized by tremors and continuous twitching movements of her left eye.

Her neurological examination revealed normal forehead wrinkling and the patient's ability to elevate the right eyebrow was intact. However, she had an obvious right-sided facial droop at rest with loss of her right nasolabial fold. She also had an asymmetrical smile on examination (Figure 2). External ear examination did not reveal any vesicular rash, scabbing, erythema, or discharge. There was no associated peri-auricular vesicular rash, lesion, or pain, so Ramsay Hunt syndrome was excluded. There was no taste disturbance or hyperacusis. The rest of her neurological and systemic assessment was unremarkable. Of note was an interval marked reduction in the size of gingival overgrowth (GO) and slight decrease in hirsutism had occurred.

Neurotoxicity due to CNIs has been reported for both tacrolimus (TAC) and cyclosporine (CsA). With TAC, neurotoxic side effects include tremor, headache, neuralgia, agitation, motor weakness, and seizures [21]. Among patients who use TAC, from 25% to 31% of them develop some form of neurotoxic manifestations. About 20% of patients have mild neurological complications including tremors (most frequent condition), insomnia, headache, vertigo, dysesthesias, photophobia, and mood change [22]. In one prospective study of 294 patients, major neurological side effects were identified in 16 (5.4%) of the patients. These side effects were related, in many instances, to high plasma levels of tacrolimus [23]. In our patient, the tacrolimus trough level was in the normal range at 15 ng/mL (therapeutic range 5–20 ng/dL). The underlying mechanism of these effects is the inhibition of calcineurin (CaN) by TAC, which is profuse in the brain. CaN regulates various proteins in the brain which alter both basic brain functions and higher-order processes such as synaptic transmission and processing of memory [4].

The risk of neurotoxicity from TAC may vary according to the type of solid organ transplant received. They are rarely associated with renal transplantation [24]. However, one literature review reported eight leukoencephalopathy cases associated with renal transplantation [23]. In a few case reports involving the adult or pediatric renal transplantation literature, TAC-induced severe central nervous system or peripheral nervous system toxicity was found [22]. For patients with neurotoxicity from TAC, there are several treatment options. First, the TAC dose can be reduced, as was done in our case with a 33% dose reduction. The other optionsare a temporary hold on the administration of TAC, the stopping of TAC and switching to another CNI such as CsA, or using a CNIs-free immunosuppressant [22].

Neurologic adverse effects of CsA, in contrast to TAC, are usually mild, and most frequently manifest as involuntary fine tremors, occurring in 20–40% of patients, and often responding to a reduction in dose [24]. In patients treated with CsA, several factors appear to increase the risk of neurotoxicity. Some of these factors include advanced liver disease with failure, hypertension, hypocholesterolemia, elevated CsA blood levels, hypomagnesaemia, intravenous administration of drug, or administration of other drugs that inhibit metabolism of the CsA [22].

4. Conclusions

This case report involved multiple significant ADRs due to CNIs in a single patient who had undergone a renal transplant for end-stage kidney failure. We presented details relating to the three major ADRs associated with the use of the CNIs experienced by this patient. These were gingival hyperplasia (GH), hypertrichosis, and neurotoxicity.

When using a CNI such as cyclosporine A, the concomitant use of a CCB significantly increases the risk of GH. Thus, CCBs should be avoided, or if in use, be discontinued and replaced with other anti-hypertensive drugs. Furthermore, patients using cyclosporine must be educated about the potential complications of hypertrichosisas well as GH, and regular follow-up to monitor side effects and cyclosporine levels are of utmost importance if complications are to be prevented. In patients who are worried about developing cosmetic side effects such as hypertrichosisdue to cyclosporine, switching them to tacrolimus may be advised. However, it should be kept in mind that tacrolimus has significant neu-

rological complications, and patients must be educated to seek medical attention should these develop.

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Informed Consent Statement: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

Cyclosporine (CsA), end-stage renal disease (ESRD), calcineurin inhibitor (CNI), gingival hyperplasia (GH), tacrolimus (TAC), calcium channel blockers (CCBs).

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