Hypertrophic Cardiomyopathy secondary to Tacrolimus in a kidney transplant patient: A case report and focused review of the literature

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April 26, 2022

Abstract

In receptors of solid organ transplant, calcineurin inhibitors has become a pillar of immunosuppressive treatment. Several case reports have shown hypertrophic and dilated cardiomyopathy as a side effect of tacrolimus. We present the case of a woman receptor of a kidney transplant who developed hypertrophic cardiomyopathy due to Tacrolimus.

Introduction:

Solid organ transplantation is a complex phenomenon made possible by our better understanding of the immune system and the technological advances of modern medicine. Transplantation carries an intrinsic risk of graft-rejection that must be controlled. For this reason, immunosuppressive therapy is always initiated in these patients[1]. Among the immunosuppressive drugs used in solid organ transplantation, calcineurin inhibitors (CNIs), primarily Tacrolimus, have proven an effective and relatively safe option for these patients, with low rates of graft-rejection [1].

However, patients taking Tacrolimus are not exempt from adverse effects, some of which can be potentially life threatening, if they're not identified early. Some of the most important side effects described in medical literature include nephrotoxicity, high blood pressure, post-transplant diabetes mellitus (PTMD), new-onset diabetes after transplantation (NODAT), dyslipidemia, and modification of cardiovascular-risk profile [2]. Also, multiple electrolyte disorders as hyperkalemia, hypomagnesemia, hypercalciuria and metabolic acidosis have been described [3]. Cardiovascular side effects as NODAT, dyslipidemia and hypertension with clinically significant increase and consequently an increment in the risk of stroke, myocardial infarction and heart failure have been described [4].

Tacrolimus - induced cardiomyopathy is an uncommon but important cardiovascular side effect of this drug, which has been described predominantly in pediatric transplant receptors [5]. However, it has been also reported in adults receptors of renal, hepatic, cardiac and small bowel transplantation [6-9]. Hypertrophic cardiomyopathy due to Tacrolimus has been cataloged as non familial acquired cardiomyopathy by the European Society of Cardiology (ESC) [10], while the American Heart Association (AHA) classifies it as a secondary cardiomyopathy [11].

Case description

A 65-year-old woman with a history of hypertension, diabetes, and chronic kidney disease secondary to polycystic renal disease was the subject of a cadaveric-donor kidney transplantation. Pre-transplant electrocardiogram and echocardiogram were reported as normal. Immunosuppressive therapy was initiated with tacrolimus and (besides a short period of time when it was suspended due to medication related tremors) was administered uninterruptedly for five years without novelty. During this time, tacrolimus plasma levels remained within a range of 5.1-11.2 ng/mL (medium of 6.39 ng/mL).

In her fifth year of treatment, the patient developed lipothymia as well as dyspnea with physical activity, asthenia and adynamia. Due to her symptoms, a new echocardiogram was performed, which revealed findings compatible with obstructive hypertrophic cardiomyopathy: interventricular septum thickness of 15 mm and a left ventricular posterior wall thickness of 11 mm (Figure 1) coupled with left ventricular outflow tract obstruction signs (Figure 2 and 3) confirmed by an end -systolic gradient (64 mmHg) in continuous Doppler through the left ventricular outflow tract. No significant variants were detected in the panel testing for genes ACTC1 (sarcomere gene), FLNC, LAMP2, MYL2 (sarcomere gene), PRKAG2 (related with glycogen storage disease), TNNI3 (sarcomere gene), TTR, CSRP3, GLA (related with Fabry disease), MYBPC3 (sarcomere gene), MYL3, PTPN11, TNNT2 (sarcomere gene), DES, JPH2, MYH7 (sarcomere gene), PLN, TNNC1, TPM1 (sarcomere gene) which are related with genetic Hypertrophic Cardiomyopathy.

Initially considering surgical myectomy and cardiac resynchronization therapy as measures to improve patient's quality of life, a coronary arteriography was performed with findings of moderate coronary artery disease which was treated with stents placed in her right coronary and circumflex arteries. Nevertheless, patient's symptoms worsened, and echocardiographic findings progressed. A review of the medical literature arose consideration of the possibility that tacrolimus use was the cause of our patient's obstructive cardiomyopathy and medication was discontinued. After switching immunosuppression therapy to an mTOR inhibitor (sirolimus), symptoms resolved after about 1 year, and echocardiographic findings reversed progressively after 2 years.

Discussion

A relationship between blood levels of Tacrolimus and an increasing thickness of left ventricular wall have been described more frequently with blood levels above 15 ng/mL, however it was also significant with blood levels between 10 and 15 ng/mL and below 10 ng/mL as in our case[5]. Also, these patients, usually present nonspecific symptoms such as asthenia, adynamia and lipothymia. However, a wide variety of signs and symptoms related with congestive heart failure as dyspnea, orthopnea, anorexia, fatigue, tachypnea, tachycardia, pulmonary edema and hepatomegaly have been described [8,12].

Epidemiology

We conducted a review of the medical literature available in a number of major clinical databases (PubMed, New England Journal of Medicine, JAMA, Nature, Annals of internal Medicine, Google Scholar and SciELO). We found 18 articles, consisting of case reports and observational studies, which described Hypertrophic Cardiomyopathy as a side effect of Tacrolimus occurring in a wide age range (Table 1). While similar cases have been described in patients aged between 58 to 62 years[8,13,14], there are reports of this adverse effect occurring in much younger patients. For example, Turska et al. mention a 17-month-old child with hypertrophic cardiomyopathy[15], and another case describes a premature newborn with hypertrophic cardiomyopathy whose mother had received tacrolimus during pregnancy [16]. There were no differences between men and women regarding occurrence of tacrolimus induced cardiomyopathy, with reports of this adverse effect in both sexes.

Clinical presentation

Several cases presenting dyspnea, fatigue and symptoms and signs due to obstructive Hypertrophic Cardiomyopathy have been described[8,12]; while our patient main complaint was lipothymia, these other symptoms were also present. Less frequently, asymptomatic cases have been reported, with clinical presentation being a new heart murmur identified during follow up [17,18]. Although hypertrophic cardiomyopathy due to

tacrolimus is the most frequent type of cardiomyopathy described, few cases of dilated cardiomyopathy have been also described [19,20].

Therapeutic approach

Possibly, because hypertrophic myocardiopathy secondary to tacrolimus is a rare adverse effect, currently there are no guidelines indicating how it should be treated. However, several case reports and observational studies have shown reversal of this side effect with tacrolimus suspension and replacement with another immunosuppressive drug such as Cyclosporine or an mTOR inhibitor [14,17,18,20-22]. After switching immunosuppressive therapy to sirolimus, our patient symptoms and echocardiographic findings resolved.

Conclusion

Hypertrophic Cardiomyopathy secondary to Tacrolimus is an uncommon potential life-threatening adverse effect described in solid organ transplant receptors receiving this calcineurin inhibitor. Thus, physicians should pay attention to patients receiving this drug, especially when symptomatic patients are detected, in order to allow a proper diagnosis of a potential cardiomyopathy and to establish accurately its management and treatment, because it has been observed that this adverse effect is reversible with its suspension.

Author contributions

Guillermo Hernández Silva: Studied the conception and designed the study, also reviewed the manuscript.

Ricardo Giovanni Puerto Chaparro: Studied the conception and designed the study, also reviewed the manuscript.

Javier Álvaro Martínez Melo: Studied the conception and designed the study, also reviewed the manuscript.

Cristian Orlando Porras Bueno: Wrote, reviewed the manuscript and also was involved in acquisition of data and analysis of data.

Javier Eduardo Martínez Rodríguez: Wrote, reviewed the manuscript and also was involved in acquisition of data and analysis of data.

Sharon Julieth González Trillos: Wrote, reviewed the manuscript and also was involved in acquisition of data and analysis of data.

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Figures

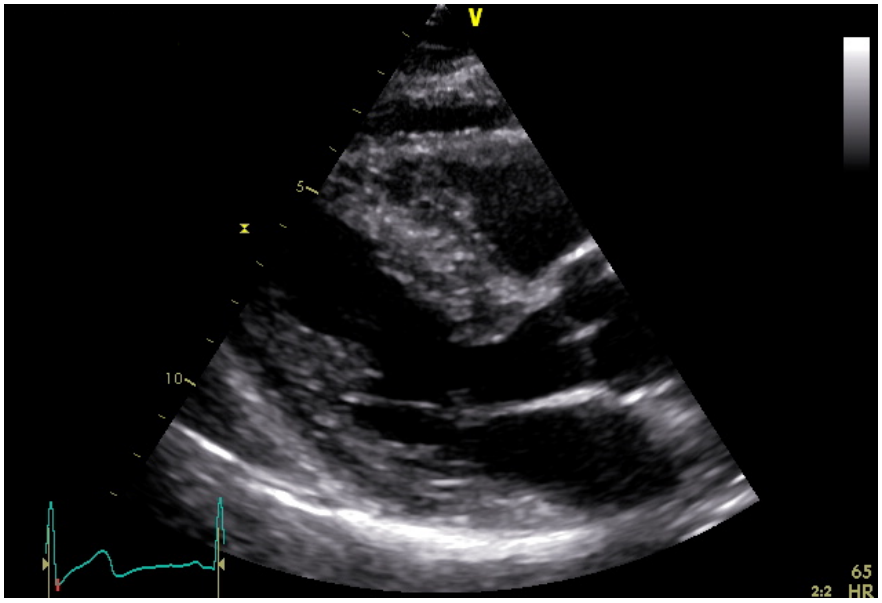


Figure 1. Longitudinal parasternal end - diastolic plane: Asymmetric septal hypertrophy (interventricular septum thickness 15 mm).

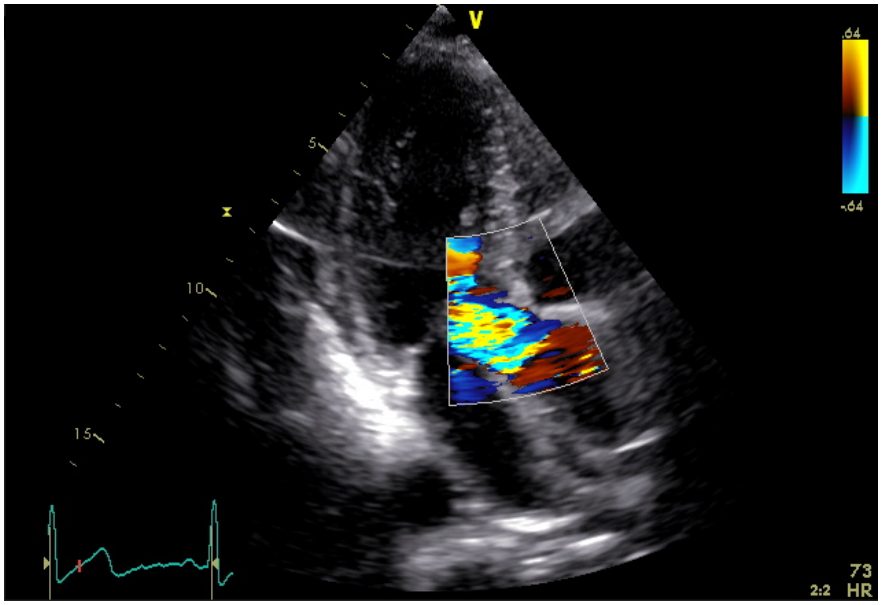


Figure 2. Apical mid-systolic long-axis view: Systolic turbulence in the left ventricular outflow tract.

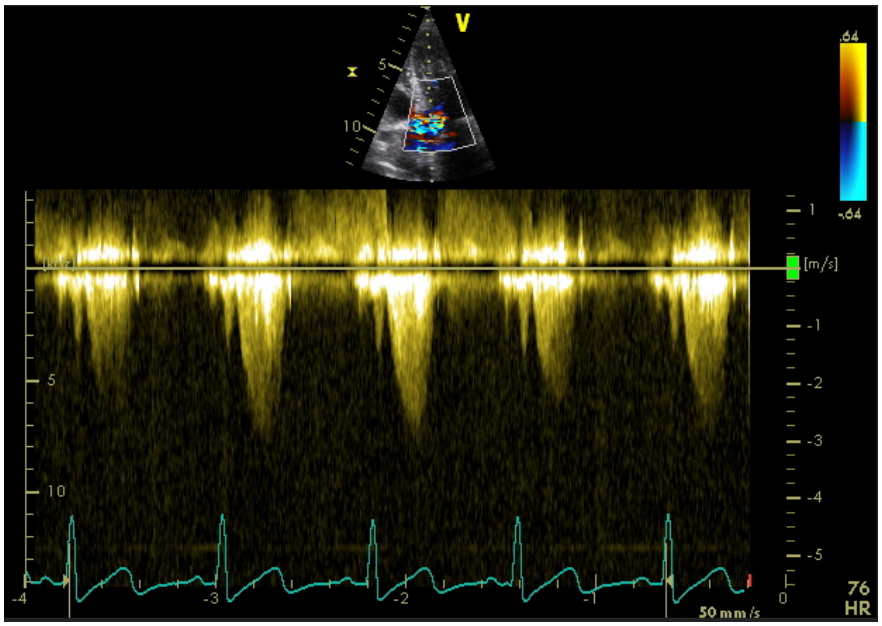
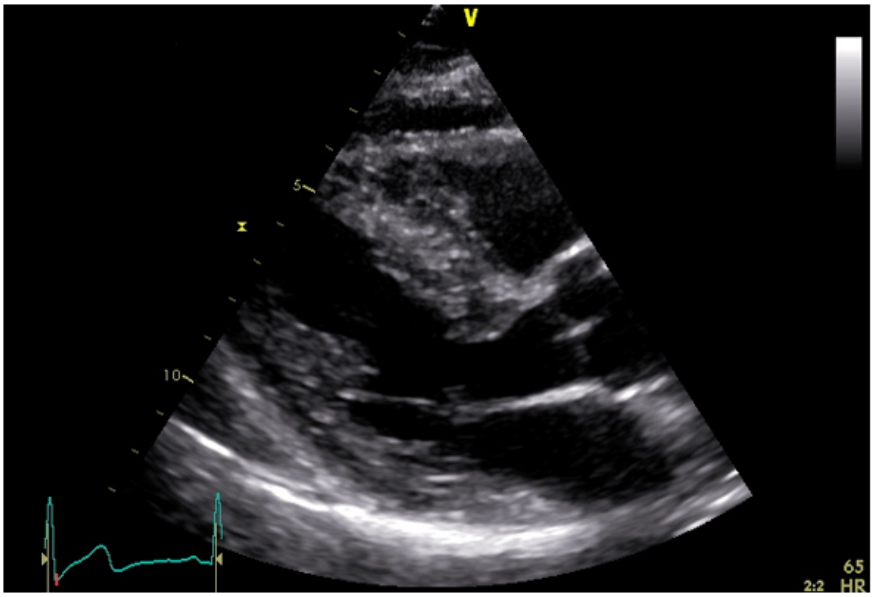


Figure 3. Continuous Doppler through the left ventricular outflow tract: end -systolic gradient of 64 mmHg.



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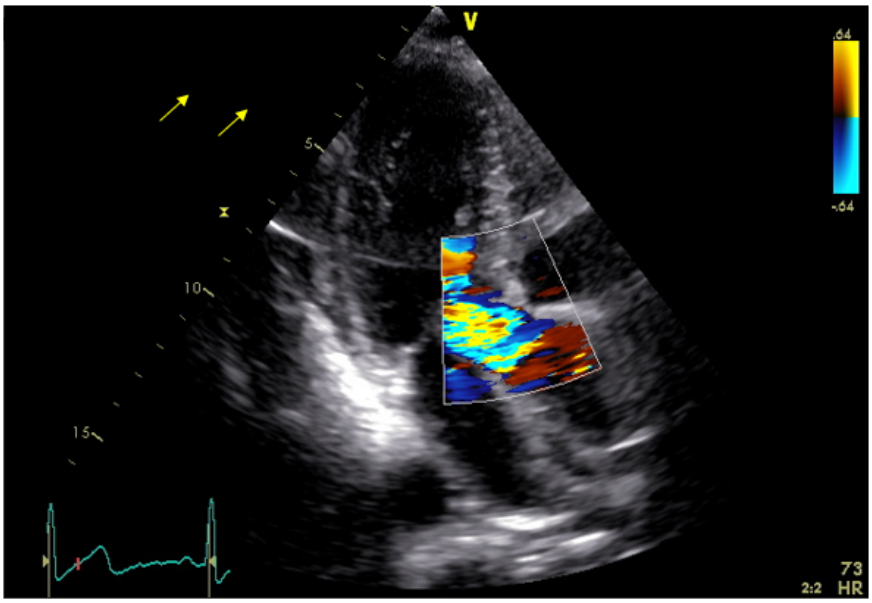

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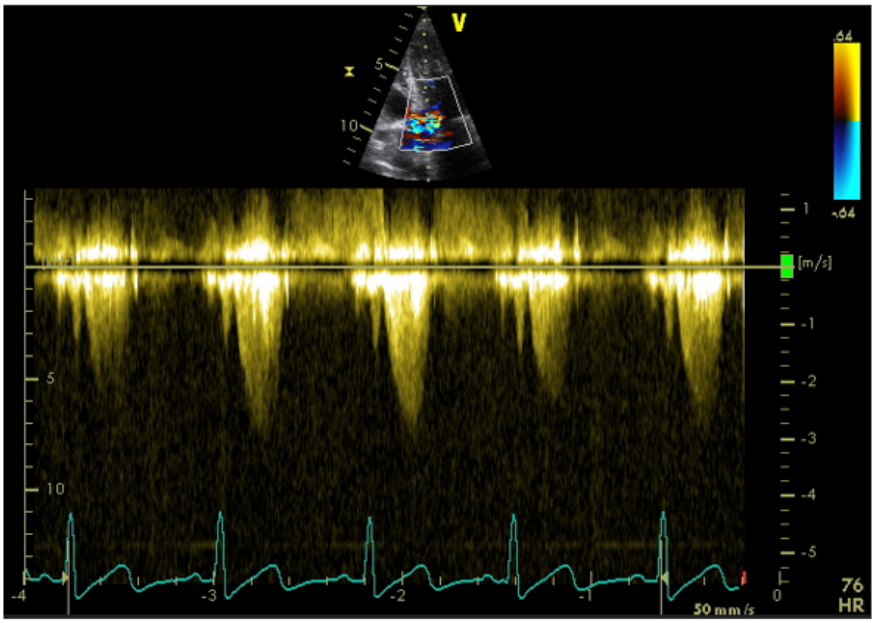

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