RHEUMATOLOGY

Letter to the Editor (Case report)

doi:10.1093/rheumatology/kex310

Tacrolimus-induced hypertrophic cardiomyopathy in a patient with dermatomyositis

Rheumatology key message

- Hypertrophic cardiomyopathy can occur in autoimmune disease patients who are treated with tacrolimus.

SIR, Tacrolimus is a strong immunosuppressant that was discovered in the soil of Mount Tsukuba, a Japanese mountain, in 1984 [1]. It binds to FK binding protein 12 (FKBP12) in the cytoplasm to form a complex. The complex binds activated calcineurin and inhibits the activation of T cells [2]. It was initially used to prevent organ rejection in transplant recipients [3]. Recently, it has also been used to treat autoimmune diseases, including RA, LN and DM- or PM-associated interstitial lung disease (ILD).

We herein report a case of hypertrophic cardiomyopathy (HCM) in a patient receiving tacrolimus for the treatment of DM-associated ILD. Tacrolimus was reported to improve PM-associated ILD in 1999 [4], and it was approved for the treatment of DM- and PM-associated ILD by Japan's Ministry of Health, Labour and Welfare in 2013. Kidney impairment, hyperglycaemia and hyperkalaemia are well known as typical side effects of tacrolimus [5]. Tacrolimus-induced HCM is also known to be an extremely rare side effect in transplant recipients [6]. However, to the best of our knowledge, there have been no reports of tacrolimus-induced HCM in patients with autoimmune disease.

In March 2013, a 61-year-old Japanese woman was referred to our department after experiencing palpitation on exertion. Five years earlier, she had been diagnosed with DM. Treatment for myositis with prednisolone (PSL; 40 mg/day) had been initiated, and then slowly tapered to 5 mg/day. Three years earlier, she developed ILD and the PSL dose was increased from 5 to 40 mg/day, with tacrolimus (1 mg/day). This led to the improvement of her ILD. The PSL dose was then tapered to 5 mg/day and the dose of tacrolimus was increased to 2 mg/day. Five months earlier, her ILD relapsed and the PSL dose was increased from 5 to 60 mg; the tacrolimus dose was also increased from 2 to 5 mg/day. Thereafter, her ILD symptoms improved. An ECG showed ST-segment depression with T-wave inversion in I, aVL and V2–6. She was admitted to our hospital to evaluate the possible diagnosis of coronary artery disease. A physical examination revealed the following findings: body temperature, 36.5 °C; blood pressure, 125/81 mmHg; and pulse, 87 beats per minute and regular. Her heart sounds were clear without audible murmurs. Fine crackles were audible in the bilateral lower lung fields. There was no skin rash or muscle symptoms. A laboratory examination showed a normal serum level of creatine kinase, and elevated plasma levels of brain natriuretic peptide (364.6 pg/ml; normal range <18.4 pg/ml). The trough level of tacrolimus in the patient's blood was 6.6 ng/ml. Transthoracic echocardiography (TTE) showed asymmetric septal hypertrophy (interventricular septum, 13.4 mm; left ventricular posterior wall thickness, 8.6 mm), a preserved systolic function with a left ventricular ejection fraction of 61.8% and no left ventricular outflow tract obstruction.

Coronary angiography revealed no evidence of coronary artery disease. Cardiovascular magnetic resonance revealed diffuse hypertrophy of the left ventricular wall (Fig. 1A). The interventricular septum thickness had increased from 8 to 13.4 mm and the left ventricular posterior wall thickness had increased from 7.8 to 8.6 mm on TTE compared with the findings observed 1 month before hospitalization. Her trough level of tacrolimus was high (>10 ng/ml) after hospitalization. Tacrolimus-induced HCM has been reported to correlated with the tacrolimus blood levels [7]. We therefore suspected tacrolimus-induced HCM. Tacrolimus was discontinued and treatment with ciclosporin was initiated, which led to the complete disappearance of her palpitations. The abnormal ECG changes began to improve within a month, and the HCM on TTE and cardiovascular magnetic resonance images regressed within 9 months after the discontinuation of tacrolimus (Fig. 1B).

The patient has had no history of hypertension, aortic valve stenosis and no family history of HCM. We considered DM-associated cardiomyopathy to be less unlikely because the disease activity was completely controlled. Her TTE and ECG findings were normal in 2008 before the initiation of tacrolimus. Furthermore, the discontinuation of tacrolimus led to the improvement of HCM. Thus, we concluded that tacrolimus caused HCM in our case.

The following pathogenesis of tacrolimus-induced HCM has been proposed. FKBP12 inhibits the release of calcium from the sarcoplasmic reticulum. Due to the binding of tacrolimus to FKBP12 in the cardiomyocytes, FKBP12 does not bind to the sarcoplasmic reticulum; consequently, the release of calcium from the sarcoplasmic reticulum increases causing the excessive contraction of the cardiomyocytes [8].

In this case, HCM was detected by ECG with an initial presentation of palpitation. However, in several cases of tacrolimus-induced HCM, the patients remain asymptomatic in transplant recipients [7]. Although HCM is an extremely rare side effect of tacrolimus, when it occurs it can be reversible. Regular check-ups to detect cardiac side effects should be considered when patients with autoimmune disease are treated with tacrolimus.

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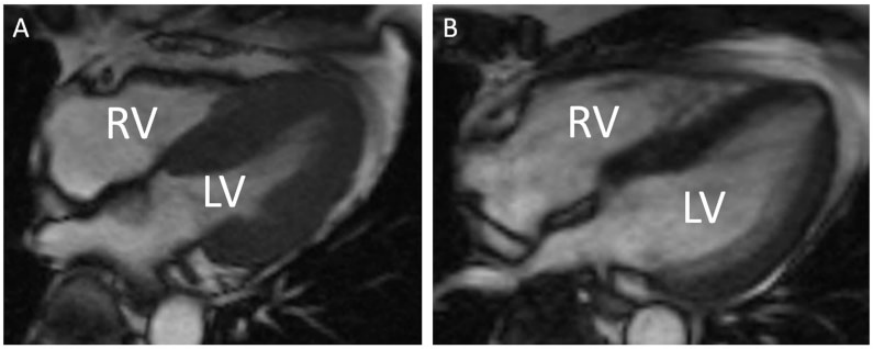
Fig. 1 Cardiovascular magnetic resonance images from a DM patient with tacrolimus-induced hypertrophic cardiomyopathy



(**A**) Four-chamber long-axis CMR images obtained during hospitalization showed an increase in the left ventricular wall thickness and a decrease in the left ventricular cavity. (**B**) Four-chamber long-axis CMR images obtained 9 months after the discontinuation of tacrolimus showed improvement of the left ventricular hypertrophy and a decrease in the left ventricular cavity. CMR: cardiovascular magnetic resonance; LV: left ventricle; RV: right ventricle.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

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Revised version accepted 6 July 2017
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