Tacrolimus Related Brady and Tachyarrhythmias in a Familial Amyloid Polyneuropathy Patient who Underwent Partial Liver Transplantation

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Liver transplantation has become a valuable treatment for FAP and tacrolimus is highly effective for the prevention of liver allograft rejection. Recently, tacrolimus-induced sinus bradycardia and QT prolongation with ventricular tachycardia have been reported, though no relationship to the plasma concentration of tacrolimus was suggested. On the 80th day after both liver transplantation and the start of tacrolimus administration, our patient experienced syncope. An ECG taken immediately revealed an additional right bundle branch block and the QT interval prolongation (corrected QT interval was 509 msec, which had slightly increased compared to 4 days before). The next day she suffered another attack and ECG monitoring disclosed wide QRS tachycardia (240 beats/minute). On the 82nd day wide ORS tachycardia (206 beats/minute) reappeared. During the following one week she suffered two episodes of dizziness and ECG showed marked bradycardia (35 beats/minute). Sinus bradycardia or sinoatrial block was suspected. In our patient the occurrence of transient RBBB, marked bradycardia (possibly sinoatrial block) and wide QRS tachycardia were considered to possibly be due to conduction block caused by the use of tacrolimus. Because brady-and tachyarrhythmias have been newly developed after liver transplantation under the tacrolimus regimen, and the tachyarrhythmias have diminished after changing the tacrolimus administration to cyclosporin, we speculate that brady-and tachyarrhythmias were thus possibly caused by tacrolimus. In addition, the amyloid heart in FAP might be more sensitive to the intracellular calcium accumulation effect of tacrolimus, because the administration of tacrolimus does not result in an overdose based on the doses and trough levels of tacrolimus.

Keywords —— tacrolimus, cardiac arrhythmia, liver transplantation

Introduction

Tacrolimus is a potent immunosuppressive agent and a calcineurin inhibitor, which has recently come into clinical use as an anti-rejection agent in the field of transplantation therapy. The side effects of this drug closely resemble those of cyclosporin, including tremor, headache, paresthesia, blurred vision, photophobia, tinnitus, nausea, vomiting, hypertension, hyperglycemia, hyperkalemia and hyperuricemia. Cardiac complications of tacrolimus have been reported in the form of cardiac hypertrophy, bradyarrhythmias and tachyarrhythmias. In this communication we describe a familial amyloid polyneuropathy (FAP) patient who received partial liver transplantation and suffered from brady-and tachycardia possibly caused by tacrolimus.

Materials and Methods

1. Case Report

The patient was a 47-year-old woman with a 7-year history of FAP, who presented with polyneuropathy and auto-
nomic disturbances. Amyloid deposition was seen on rectal biopsy and DNA analysis showed an abnormal transthyretin with a valine to methionine substitution at position 30. Routine laboratory tests including renal function were unremarkable. Electrocardiogram (ECG) revealed left axis deviation, first-degree AV block, corrected QT interval (QTc) of 447 msec and QS waves in leads V1 - V3 (Fig. 1 A), all of which are characteristic findings of amyloid heart in FAP. Echocardiography showed left ventricular symmetrical thickening and normokinesis. After the approval from the ethics committee of the university she underwent partial liver transplantation using a graft from a living donor. After transplantation, oral methylpredonisolone 10mg and tacrolimus 3.2mg to 5.6mg/day b.i.d were added for immunosuppression to oral sulpiride 300mg/day, rebamipide 300mg/day and droxidopa 600mg/day. On the 77th day, an ECG showed QTc of 498 msec.

On the 80th day she experienced syncope. ECG taken immediately revealed additional right bundle branch block and QTc was 509 msec (Fig. 1 B). The next day she suffered another attack and ECG monitoring disclosed wide QRS tachycardia (240 beats/minute). On the 82nd day wide ORS tachycardia (206 beats/minute) reappeared (Fig. 1 C). All laboratory data, including hematocrit, serum potassium and albumin, did not remarkably change in last 4 weeks and cardiac function on echocardiography was well preserved.

2. Assay of tacrolimus

Trough blood tacrolimus concentration were assayed using microparticle enzyme immunoassay (MEIA) and an IMx autoanalyzer. Tacrolimus dosage was adjusted to attain a trough blood concentration ranging from 10 to 18 ng/mL.

3. Clinical course and drug administration

During the following one week she suffered two episodes of dizziness and ECG showed marked bradycardia (35~46 beats/minute; Fig. 1 D). Sinus bradycardia or sinoatrial block was suspected. Although the morning trough levels of tacrolimus were not very high (Table 1), this drug was suspected of producing the life-threatening arrhythmia and was discontinued on the 82nd day. From the 83rd day oral cyclosporin 150 to 200mg b.i.d were newly added to her predonisolone. Since then, tachyarrhythmias have not recurred (Fig. 2). ECG showed QTc of 482~490 msec. Permanent pacemaker was implanted on the 89th day for prolonged sinus bradycardia.

**Discussion**

Potentially toxic effects of tacrolimus on the heart were

| Table 1. Tacrolimus Morning Trough Levels and Electrolyte Balance. |
|-------------------------|--------|--------|--------|--------|--------|
| Postoperative days      | 76th   | 80th   | 81st   | 82nd   | 83rd   |
| tacrolimus (ng/mL)      | 13.7   | 13.0   | 13.3   | 11.5   | 15.6   |
| serum Na (mEq/L)        | 131    | 136    | 136    | 138    | 135    |
| K (mEq/L)               | 4.9    | 4.1    | 3.5    | 3.9    | 3.5    |
| Cl (mEq/L)              | 94     | 100    | 99     | 101    | 99     |
| Hematocrit (%)          | 25.8   | 26.0   | 25.4   | —      | 27.5   |
| Albumin (g/dL)          | 3.2    | 3.1    | 3.1    | 3.2    | 3.1    |

Fig. 1. A: ECG on Admission. B: ECG on the 80th Day. C: ECG on 82nd Day Showing Ventricular Tachycardia. D: ECG on 85th Day Showing Marked Sinus Bradycardia.
demonstrated experimentally in rabbits\(^8\) and baboons\(^9\), and chest discomfort and/or palpitation have occasionally been reported in humans\(^10\). In addition, clinically apparent cardiotoxicity was described in five pediatric transplants showing hypertrophic cardiomyopathy\(^11\), which almost resolved after discontinuation of tacrolimus. Recently tacrolimus-induced sinus bradycardia\(^3\) and QT prolongation with ventricular tachycardia\(^4,12\) were reported, though no relationship to the plasma concentration of tacrolimus was suggested. Tacrolimus has been shown to increase in the intracellular calcium\(^2,3\) and to prolong the action potential duration, which might induce the prolongation of conduction and result in conduction block. In our patient transient RBBB, marked bradycardia (possibly sino atrial block) and wide QRS tachycardia were possibly due to conduction block caused by the use of tacrolimus. Because tachyarrhythmias have newly developed on 80th day after liver transplantation with tacrolimus regimen, and have diminished after change of tacrolimus administration to cyclosporin, we speculated that tachycardia were possibly caused by tacrolimus. Because sinus bradycardia, however, had prolonged one week after tacrolimus cessation, we thought it possibly persistent and decided to implant permanent pacemaker.

Liver transplantation has become a valuable treatment for FAP and tacrolimus is highly effective for the prevention of liver allograft rejection. When tacrolimus is used in FAP patients with amyloid heart, however, cardiac side effects including arrhythmia need to be monitored very carefully.

References


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