Thrombolytic Therapy in a Heart Transplant Recipient with Acute Myocardial Infarction

Ehud I. Goldhammer MD[1,2], Leonid Kharash MD, PhD[1] and Edward G. Abinader MD[1,2]

[1]Department of Cardiology, Bnei-Zion Medical Center, and [2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Key words: acute myocardial infarction, heart transplant, thrombolytic therapy

IMAJ 1999;1:198–199

Coronary graft arteriosclerosis is the limiting factor in the long-term survival of heart transplant recipients [1–3]. Diagnosed by angiography in 40–50% of patients within 5 years of transplantation, the disease is characterized by diffuse proximal and distal narrowing — with or without abrupt terminations of the arteries. Coronary angioplasty, atherectomy, stenting and bypass surgery for coronary artery narrowing in heart transplant recipients have been widely used and with considerable success [4]. Successful thrombolysis in a heart transplant recipient has been reported only once to date [5]. We report here the positive outcome of thrombolytic therapy in a heart transplantation survivor who presented with an acute myocardial infarction.

Case Description

A 56-year-old male presented to the intensive cardiac care unit with retrosternal pain and pressure radiating to the left arm that had begun 3 hours before his arrival. The chest pain was constant and associated with diaphoresis and nausea. Four years previously he had received a heart transplant due to ischemic cardiomyopathy. His post-transplantation course had been relatively benign with only mild episodes of early rejection. During the year prior to the present admission he had suffered from effort-related dyspnea and had undergone percutaneous transluminal angioplasty twice (to the mid-left anterior descending artery). On admission, blood pressure was 190/90 mmHg, pulse 88 regular, respirations 18/min, and temperature 36.8°. Physical examination was unremarkable except for an apical holosystolic murmur 2/6 and a fourth heart sound. The initial electrocardiogram revealed 5 mm ST segment elevations in leads II, III, and aVF, aVR and V4R consistent with an acute inferior wall and right ventricular infarction. Intravenous treatment with heparin and isosorbide mononitrate was initiated along with RESCUPASE® (Grunenthal, Germany; saruplase; unglicosylated human single-chain urokinase-type plasminogen activator). Within 30 min of saruplase therapy the patient's pain subsided and repeated ECGs showed gradual return of ST segment to the isoelectric line with evolution of T wave inversions in the same ECG leads.

At 6 h after initiation of thrombolysis and 9 h from pain onset, creatine kinase measured 1,197 u/L, MB fraction 22% and troponin I 6.5 (normal range 0–1.5). The patient was maintained on intravenous isosorbide mononitrate and heparin for 48 h, followed by subcutaneous low molecular weight heparin and oral nitrates. His usual immunosuppressive therapy was continued concomitantly, namely prednisone, azathioprine and cyclosporine. The hospital course was uneventful and the patient was discharged home on the seventh day. Three weeks after discharge, cardiac catheterization revealed two-vessel disease, a long proximal 50–60% right coronary artery lesion and a long 50–60% mid-distal LAD[1] lesion; therefore neither balloon angioplasty nor bypass surgery was suggested.

Comment

Graft coronary disease may occur quite rapidly after cardiac transplantation in both children and adults. Characteristic features include concentric and longitudinal internal proliferation, often with intact elastica and media of the coronary arteries — unlike the "common" coronary atherosclerotic changes with asymetric plaques and calcifications. The latter may also be found in long-term transplant survivors of more than 10 years.

The cause of the accelerated graft atherosclerosis remains controversial and is probably multifactorial. Male sex of donors, the older age of donors and recipients (45–54 years), a preoperative diagnosis of coronary artery disease, as well as a high level of triglycerides are considered independent strong predictors of graft atherosclerosis. Other factors associated with increased risk of graft CAD[2] include the increased number of early and late postoperative rejection episodes — especially after the first year — and increased dosages of prednisone, requiring augmentation of immunosuppression. On the other hand, cyclosporins seem to confer a protective effect. An additional risk factor is the angiotensin-converting enzyme genotype of the donor organ; moreover, a negative association has been found between the development of transplant CAD and the I allele in the donor. Several studies have indicated that this type of CAD is associated with donor-specific cell-mediated alloreactivity to vascular endothelium. Humoral immunity does not appear to have a role in this disease.

The reason why graft CAD is often difficult to diagnose is that typical angina is uncommon and can easily be missed, especially during the first years following transplantation because the cardiac allograft is denervated and lacks afferent innervation. However, there is growing evidence for both sympathetic and sensory reinnervation in long-term transplant survivors. The presence of effort dyspnea, fatigue, and functional class deterioration should raise the suspicion of graft CAD. Echocardiography may reveal wall motion abnormalities suggestive of ischemia and/or silent infarctions. Repeated coronary angiographies and angioscopies are necessary to assess CAD development and progression and for determining reperfusion methods. PTCA[3], stents, atherectomy and coronary artery bypass surgery have already been performed successfully in hundreds of patients [5]. Diagnosis of acute infarction is difficult and is often made retrospectively, following the appearance of Q waves in the ECG or wall motion abnormalities in the echocardiogram, congestive heart failure, shock or death. This is probably the reason why only one case of successful thrombolytic treatment in a heart transplant recipient has been reported.

Thrombolysis is indicated when the clinical and ECG criteria are met. Thrombolysis in transplant patients is especially indicated because fibrinolysis in transplanted human hearts has been shown to be altered and deficient. Biopsy specimens obtained from recipients of cardiac allografts revealed depletion of tissue plasminogen activator in arteriolar smooth muscle cells and elevated levels of t-PA[4] and plasminogen activator inhibitor.

A similar case was described by Virk et al. [5], and their case and ours share some common features. In both patients the initial post-transplant years were relatively uneventful with only a few mild rejection episodes, however there was angiographic evidence of progressive coronary artery prior to the acute infarction. In both cases, the clinical manifestations of the acute infarction were typical and not blunted by the above-mentioned mechanisms; this prompted rapid ECG recording with consequent diagnosis and thrombolytic treatment.

It should be borne in mind, however, that in most transplant patients the use of thrombolytic agents has likely been limited by the atypical clinical presentation of cardiac ischemia. Currently, transplant patients are typically followed at institutions with highly trained cardiology and cardiac surgery personnel. Clearly, emergency department physicians in primary and secondary referral hospitals should be alert to the fact that transplant patients may suffer an acute myocardial infarction with or without the characteristic chest pain or discomfort. Finally, since thrombosis may be involved in the precipitation of acute infarction, physicians should not refrain from using thrombolytic agents.

References

1. Gao SZ, Alderman EL, Schroeder JS, Silverman JF, Hunt SA. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. *J Am Coll Cardiol* 1988;12:334–40.
2. Miller LW. Long term complications of cardiac transplant. *Prog Cardiovasc Dis* 1991;33: 229–82.
3. O'Neill BJ, Pflugfelder PW, Singh NR, Menkis AH, McKenzie FN, Kostuk WJ. Frequency of angiographic detection and quantitative assessment of coronary arterial disease one and three years after cardiac transplantation. *Am J Cardiol* 1989;63:1221–6.
4. Halle AA 3rd,Wilson RF, Massin EK, Bourge RC, Stadius ML, Johnson MR, Wray RB, Young JB, Davies RA, Walford GD, et al. Coronary angioplasty in cardiac transplant patients: Results of a multicenter study. *Circulation* 1992;86:458–62.
5. Virk AS, Antosia RE, Patridge RA. Use of thrombolytic therapy in a heart transplant recipient with acute myocardial infarction. *Ann Emerg Med* 1995;25:548–50.

Correspondence: Dr. E. Goldhammer, Dept. of Cardiology, Bnei-Zion Medical Center, 47 Golomb St., Haifa 31048, Israel. Tel: (972-4) 835 9702; Fax: (972-4) 835 9225; email: egoldh@sitcom.co.il.

[1] LAD = left anterior descending artery
[2] CAD = coronary artery disease
[3] PTCA = percutaneous transluminal angioplasty
[4] t-PA = tissue plasminogen activator

Capsule

Anti-malarial drugs pathway

The search for new anti-malarial drugs is being pushed by the increasing development of resistance to known therapeutic agents. Jomaa et al. from Germany found that, unlike their human hosts, *Plasmodium falciparum* uses a non-mevalonate pathway (DOXP) for the biosynthesis of isoprenoids. On the basis of similarities between bacterial and algal enzymes and sequence on chromosome 14 of *P. falciparum,* the authors identified and cloned a DOXP reductoisomerase from *P. falciparum.* Plasmodia in culture and in a rodent model were inhibited by fosmidomycin, a drug known to target DOXP reductoisomerase, as well as one of its derivatives. The drugs had low toxicity and could be taken orally.

Science 1999;285:1573