

Heart Transplantation in a Patient With Systemic Mastocytosis

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Systemic mastocytosis is a hematologic disorder characterized by mast-cell proliferation and organ infiltration. A variety of stimuli and drugs can cause severe anaphylaxis in these patients. We report the case of a female patient diagnosed with systemic mastocytosis and advanced dilated cardiomyopathy in whom a heart transplant was successfully performed. *J Heart Lung Transplant* 2008;27:689–91. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

Mastocytosis is a rare hematologic disorder characterized by mast-cell proliferation and accumulation in one or more organs.¹ Systemic mastocytosis has several variants, and its form of presentation has prognostic relevance.² Indolent systemic mastocytosis is the most frequently diagnosed variant and is characterized by a benign clinical course without significant organomegaly or organ dysfunction.³ It usually manifests clinically with episodes of flushing associated with abdominal cramping, and occasionally with episodes of hypotension. Because of this “indolent” course, treatment is usually symptomatic, based on blockade of the mediator substances released by mast cells. When associated with organ infiltration, we are dealing with the smoldering sub-variant, which has an uncertain prognosis because it can evolve into more aggressive forms.⁴ In these cases, in addition to symptomatic treatment, corticoids may be indicated.⁵

The mechanism by which this disease could affect the heart and cause heart failure remains unclear. Kim et al⁶ posited that abnormally high histamine levels are associated with the development of heart failure. However, Kolck et al^{7,8} reported that neither mast-cell infiltration or continuously elevated histamine secretion caused changes in ventricular diameters or ejection fraction in their patients.

We report the case of a 56-year-old woman, diagnosed with smoldering-type systemic mastocytosis, in whom an orthotopic heart transplant was performed

for dilated cardiomyopathy. To our knowledge, this is the first reported case of its type in the literature.

CASE REPORT

A 56-year-old woman presented with a history of smoldering-type systemic mastocytosis (generalized skin lesions with enlargement of the liver and spleen). She was referred to our hospital for dilated cardiomyopathy with a left ventricular ejection fraction of 17%. She had had multiple admissions for heart failure and, on one of these admissions, she developed oligoanuric acute renal failure. The patient had a permanent pacemaker for symptomatic advanced atrioventricular block associated with chronic atrial fibrillation, which was anticoagulated with enoxaparin due to a tendency to digestive bleeding with acenocumarole. Her usual treatment consisted of diuretics, digoxin, allopurinol, enoxaparin, propafenone, enalapril, erythropoietin and iron.

Physical examination showed advanced biventricular heart failure, with jugular venous distension, bibasal rales, systolic murmur of severe mitral failure, hepatomegaly to 6 cm below the costal margin, ascites and bilateral lower-limb pitting edema. Skin examination revealed generalized, non-raised erythematous lesions, although predominantly on the anterior and posterior upper trunk. Laboratory test results are shown in [Table 1](#).

Given that the patient's clinical condition did not improve despite optimal treatment, it was decided to consider heart transplantation. As the mastocytosis itself may have been the origin of the cardiomyopathy, which could have implications for subsequent graft outcome, an endomyocardial biopsy was performed, which ruled out infiltration.

Aside from relative contraindications, such as prior renal dysfunction, the lack of reported cases in the literature on heart transplantation in systemic mastocytosis, and frequent digestive tract bleeding without significant or infiltrating lesions, no absolute contraindications were noted. Thus, the patient was included on the waiting list and transplanted on June 6, 2006.

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Table 1. Pre-transplant Laboratory Test Results

Glucose (mg/dl)	102
Creatinine (mg/dl)	1.19
Uric acid (mg/dl)	8.7
Total cholesterol (mg/dl)	144
Triglycerides (mg/dl)	85
sGOT (IU/liter)	17
sGPT (IU/liter)	19
Total bilirubin (mg/dl)	1.44
Total protein (g/dl)	7.68
Chlorine (mEq/liter)	94
Sodium (mEq/liter)	134
Potassium (mEq/liter)	4.4
Iron (μ g/dl)	102
Transferrin saturation (%)	38
Prothrombin time (s)	13.8
aPTT (s)	32.9
Fibrinogen (mg/dl)	573
NT-pro-BNP (pg/ml)	2,764

The protocol used for pre-medication and anesthetic induction was similar to that described in other cases.^{9,10} Pre-medication was performed in three steps:

1. Upon arrival to the hospital (4 hours before surgery): prednisone 90 mg intravenously.
2. One hour before induction: prednisone 90 mg, dexchlorpheniramine 5 mg and ranitidine 50 mg intravenously.
3. Thirty minutes before induction: diazepam 10 mg orally.

Anesthetic induction was performed with etomidate, using vecuronium as the neuromuscular relaxant and fentanyl as the analgesic in standard doses. Anesthetic maintenance was performed with inhaled sevoflurane. The surgical procedure was performed with the bicaval technique without incident. The patient was extubated 12 hours later with no post-operative complications and transferred to the hospital ward 5 days after transplantation.

The standard immunosuppression protocol of our center was used, consisting of oral administration of 2 g mycophenolate mofetil 4 hours before surgery and 1 g methylprednisolone intra-operatively. Induction therapy with daclizumab (1 mg/kg) was performed 4 hours after transplant and on Day 14. Maintenance immunosuppression consisted of mycophenolate mofetil 1 g every 12 hours, cyclosporine (Sandimmun, Neoral; trough levels 200 to 300 ng/ml) and deflazacort (1.5 mg/kg/day) in decreasing doses. According to the protocol of our health center, the patient was given treatment with isoniazide, cotrimoxazole, statins, oral nistatin, calcium, vitamin D and calcitonin.

The explanted organ showed dilation of all chambers and a weight of 500 g. Microscopy revealed the pres-

ence of isolated foci of fibrosis in the myocardium and interstitial inflammatory infiltrates composed of lymphocytes. Some dispersed mast cells were also observed in myocardial and valvular tissue, but with no mastocytomas being formed (accumulation of at least 15 mastocytes).¹¹ No foci of necrosis were noted.

The patient remained stable until Day 20 post-transplant at which point she developed a severe pericardial effusion with signs of cardiac tamponade, along with acute Grade 3A rejection, according to the scale established by the International Society for Heart and Lung Transplantation (ISHLT). This resolved with the administration of intravenous steroids and the creation of a pleuro-pericardial window. Subsequent follow-up assessments were normal. Two months later, the patient was admitted for lingular pneumonia with bacteremia caused by *Pseudomonas aeruginosa*. Thoracocentesis and specific antibiotic therapy were performed. Since that time, the patient has remained asymptomatic, with good graft function on all echocardiographic examinations performed. She has exhibited no evidence of mast-cell infiltration on the myocardial biopsies.

DISCUSSION

Systemic mastocytosis is an infiltrative disease that can involve the myocardium and cause heart failure. Studies in a small series of patients showed a high prevalence of diastolic dysfunction and left ventricular hypertrophy, but without changes in systolic function or ventricular diameters.⁷ However, the evidence on this topic is still very limited. Therefore, despite the fact that our patient had dilated cardiomyopathy with increased ventricular volumes and severe depression of systolic function, we decided to perform an endomyocardial biopsy to assess possible mast-cell infiltration. The absence of infiltration, in addition to diagnostic and prognostic implications (it would have made us consider changing the diagnosis to aggressive systemic mastocytosis due to the presence of organ infiltration with impairment of organ function), also has therapeutic implications, because she would have required cytoreductive treatment.³

The negative endomyocardial biopsy, confirmed by the absence of mast-cell accumulations in the explant, led us to suspect the presence of two coexisting diseases—mastocytosis and dilated cardiomyopathy—and a need for their respective treatments.

Heart transplantation is one of the most effective therapeutic options for end-stage heart failure,^{12,13} but we did not find any report of a case similar to ours. We therefore did not know what possible complications this procedure could have on patients with mastocytosis.

The first problem to be solved was planning of the surgery, because the anesthetic procedure implied the use of a series of drugs that could potentially cause mast-cell degranulation and the consequent anaphylaxis.^{9,10,14} Ad-

equate planning, based on pre-medicating the patient and using drugs that have been shown to be safe in these patients,^{9,10} allowed us to obtain a good post-operative outcome without incident.

Nevertheless, we could not predict what effect that initiation of immunosuppressive therapy would have on the course of the disease. Mastocytosis is a proliferative disorder and immunosuppressive drugs could influence its course. In principle, treatment with corticoids should not be a problem, because these drugs are used routinely in both diseases. However, there is very limited experience in this disease with other immunosuppressive agents that are used in heart transplantation, although in principle their use would appear beneficial.¹⁵⁻¹⁷ In view of the paucity of literature, and the beneficial effects that cyclosporine seems to have on mastocytosis, we chose to proceed with the immunosuppressive regimen for which we have accumulated the most experience (triple therapy with cyclosporine + mycophenolate mofetil + deflazacort), while monitoring the patient closely for any possible complications. We did not detect any progression of the patient's hematologic disease, and tryptase plasma levels decreased notably according to follow-up assessments (Figure 1).

The patient's course did not differ from that of the other patients without mastocytosis.¹³ Both the number of acute rejection episodes and infections were within the normal range and no other post-operative complications were detected. Mast cells were not observed in any of the protocol endomyocardial biopsies. This finding, along with the absence of cardiologic clinical symptoms other than the rejection episodes, documented by histology, led us to believe that the organ had become free of disease.

We conclude that in patients with smoldering mastocytosis without heart infiltration, heart transplantation

may be an option to consider as treatment for end-stage heart failure. It can be inferred that systemic mastocytosis by itself is not a contraindication for solid-organ transplantation. Adequate planning of anesthesia allows the surgical procedure to be performed without operative problems. In addition, immunosuppressive therapy seems to have a favorable effect on the course of the hematologic disease.

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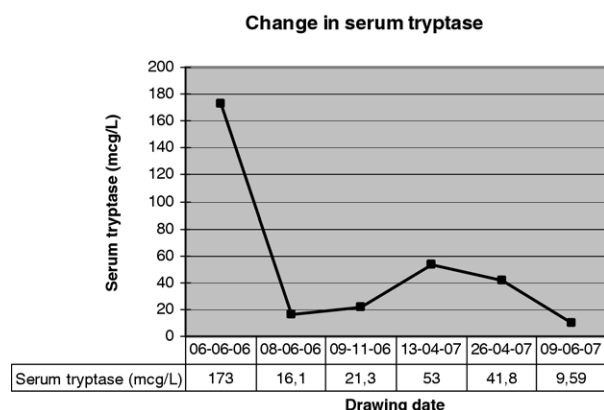


Figure 1. Change over time in serum tryptase levels. The first sample shows the control blood sample obtained before starting pre-medication for surgery.