Case 5/2008 – 44-Year-Old Male Patient that Died of Cardiogenic Shock on the 6th Postoperative Day After Orthotopic Heart Transplant

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The patient was asymptomatic and ran 8 km daily up to 42 years of age, when he started to present effort dyspnea. The symptom persisted for six months and the patient then sought medical attention in his town. The patient knew he had bronchial asthma.

The electrocardiogram (July 2003) disclosed 2:1 Mobitz type II second-degree atrioventricular block. The echocardiogram (July 2003) showed a left atrium diameter that was at the upper limit of normality and increased thickness of the interventricular septum (Table 1).

The dynamic electrocardiogram by Holter system (July 2003) showed a minimum heart rate (HR) of 33 bpm, maximum heart rate of 72 bpm. The patient showed a sinus rhythm, with 2:1 atrioventricular block. There were 46 isolated ventricular extrasystoles and 13 isolated atrial extrasystoles.

The electrophysiological study (July 2003) showed a 2:1 atrioventricular block, A-H intervals of 228 ms (normal: 55-130), H-V of 68 (N=30-55). After atrial stimulation at intervals of 600 and 550 ms, a worsening in the atrioventricular conduction was observed with a 3:1 block, with no alteration in QRS duration. An atrioventricular block with nodal and hissian involvement was diagnosed.

The coronary angiography (July 2003) did not disclose obstructions in the coronary arteries and the ventriculography was normal.

An atrioventricular cardiac pacemaker implant was carried out (August 2003). The effort dyspnea persisted.

Table 1 - Echocardiograms

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<tbody>
<tr>
<td>Aorta (mm)</td>
<td>33</td>
<td>27</td>
<td>33</td>
<td>31</td>
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<tr>
<td>Left atrium (mm)</td>
<td>40</td>
<td>45</td>
<td>46</td>
<td>48</td>
</tr>
<tr>
<td>Right ventricle (mm)</td>
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<td>44</td>
<td>41</td>
<td>Dilated</td>
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<tr>
<td>Left ventricle (LV)</td>
<td>Diastolic diameter (mm)</td>
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<td>62</td>
<td>64</td>
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<td></td>
<td>Systolic diameter (mm)</td>
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<td>55</td>
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<tr>
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<td>LV posterior wall</td>
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<td>10</td>
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</tr>
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<td>Slight</td>
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<tr>
<td>Intraventricular thrombus</td>
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<td>Yes</td>
<td>No</td>
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Key words
Cardiomyopathy, hypertrophic; cardiomyopathy, dilated; amyloidosis; shock, cardiogenic; heart transplantation.

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Nine months after the pacemaker implant, during a soccer game, the patient presented tachycardic palpitations, dyspnea and intense sudorosis with paleness and fainting sensation. A sustained ventricular tachycardia was diagnosed, which was reverted by electrical cardioversion. There was recurrence of the tachycardia one month after this episode and again electrical cardioversion was needed.

A new echocardiographic assessment (July 2004) disclosed dilation of the cardiac chambers, marked decrease in the left ventricular ejection fraction, with an image that was suggestive of apical thrombosis and moderate mitral failure (Table 1).

The patient was then referred to InCor (Instituto do Coracao – The Heart Institute) for treatment.

The physical examination (July 2004) revealed a HR of 80 bpm, BP of 100/80 mm Hg. Lung, heart and abdomen assessments were normal.

The electrocardiogram (23 of July 2004) showed a sinus rhythm, with ventricular stimulation by pacemaker triggered 200 ms after the P wave start and duration of stimulated QRS of 234 ms (Figure 1).

The electrocardiogram with inhibited pacemaker (26 July 2004) disclosed a sinus rhythm, 83 bpm, PR of 177 ms, duration of QRS 83 ms, QT of 391 ms, SAQRS + 120° backward and signs that were suggestive of left atrial overload, R wave amplitude that did not increase from V1 to V4 (Figure 2).

The chest X-ray showed a marked increase in the cardiac area. The myocardial perfusion scintigraphy (27 of July 2004) showed markedly low radiotracer uptake in the apical and anterior walls (apical and middle) and moderately low uptake in the inferior wall. The single-photon emission computed tomography (SPECT) showed diffuse hypokinesia and apical akinesia, with an ejection fraction of 35%. There was a marked lung uptake (Figure 3).

The phlebography of the left upper limb was suggestive of subclavian vein thrombosis. A diagnosis of hypertrophic cardiomyopathy was attained, with evolution to dilation, and the hypothesis of ventricular dilation caused by left ventricular desynchronization induced by QRS enlargement in the presence of stimulus via right ventricle was considered. Biventricular artificial cardiac stimulation was indicated. An atrium-biventricular and defibrillator pacemaker was implanted and the previous stimulation system was removed (23 of July 2004).

The drug therapy included captopril 75 mg, carvedilol 12.5 mg, spironolactone 25 mg, furosemide 60 mg, amiodarone 400 mg and Warfarin 2.5 mg, daily.

In spite of the changes in the stimulation and medication alterations the patient presented worsening of the dyspnea (Oct 2004), which started to occur triggered by small physical efforts, in addition to orthopnea, lower-limb edema and hepatomegaly.

The electrocardiogram (Oct 04) showed sinus rhythm, with ventricular stimulation by the pacemaker at the start and middle of the QRS (Figure 4).

The maximum O2 consumption (V O2 Max) (Oct 2004) was 12.9 ml/kg/min (normal for the age range: 40 ml/kg/min) and the slope between ventilation and CO2 production was 59.3.

The right catheterism (Dec 2004) showed the following pressures (mm Hg): right atrium: 23/19/20; right ventricle: 22/19/20; pulmonary artery: 21/16/19; pulmonary occlusion: 18. The cardiac output was 3.4 l/min and the cardiac index was 1.07 l/min/m2.

A cardiac transplant was indicated.

The patient was hospitalized for the transplant (30 March 2005); he complained of dyspnea after small efforts, BP was 100/70 mmHg, HR was 75 bpm and crackling rales were identified to the right.
Figure 2 - ECG - sinus rhythm, signs that were suggestive of left atrial overload, septal power decrease.

Figure 3 - Myocardial perfusion scintigraphy - markedly low radiotracer uptake in the apical and anterior walls (apical and middle) and moderately low uptake in the inferior wall.
The ventricular antiarrhythmic therapy capacity of the pacemaker was discontinued and 10 mg of vitamin K and 280 mg of aprotinin were administered by IV route.

The laboratory assessment (30 March 2005) disclosed hemoglobin 14.4 g/dl; hematocrit 44%, leucocytes 7200/mm³ (63% neutrophils, 2% eosinophils, 24% lymphocytes and 11% monocytes), platelets 133000/mm³, potassium 4.2 mEq/l; sodium 138 mEq/l; urea 55 mg/dl; creatinine 1.3 mg/dl INR 1.5; serologies for hepatites, HIV, cytomegalovirus, Chagas disease and toxoplasmosis were negative.

A bicaval orthotopic transplant and De Vega plastic procedure were carried out in Tricuspid Valve (30 March 2005). The patient presented total atrioventricular block (TAVB) in the operating room and the epicardial pacemaker was turned on. After an uneventful first postoperative day, the patient started to present hypotension, oliguria and vomiting.

During the postoperative evolution, the diagnoses of renal failure (creatinine 2.5 mg/dl, urea 127 mg/dl), anemia (hemoglobin 10.6 g/dl, hematocrit 32%), leukocytosis (10844/mm³, 93% neutrophils, 3% lymphocytes and 4% monocytes) and thrombocytopenia (45000/mm³), in addition to initial hyperamylasemia (887 U/l), which later decreased to 148 U/l.

The electrocardiogram showed the pacemaker stimulating atriums and ventricles (Figure 5).

The echocardiogram (4 April 2005) showed right ventricle dilation and hypokinesia, left ventricular diffuse hypokinesia with an ejection fraction of 35% (Table 1). On the sixth postoperative day, the patient presented ventricular fibrillation reverted with electrical cardioversion, with rhythm recovery, albeit without pulse and died on April 5, 2005.

Clinical aspects

A 44-year-old male patient, previously healthy, athlete, with no reports regarding his personal or family antecedents, presented for the diagnostic investigation of dyspnea.

The electrocardiogram showed a 2:1 second-degree atrioventricular block, later demonstrated to be Mobitz II at the electrophysiological study, with HV interval prolongation and worsening in the atrioventricular conduction with 3:1 block. The dynamic electrocardiogram by Holter system confirmed the maintenance of this conduction disorder throughout the day, with no evidence of associated tachyarrhythmias. The transthoracic echocardiogram disclosed an interventricular septum diameter of 15 mm and left ventricular posterior wall of 10 mm, with no indication of pressure gradients in the left ventricular outflow tract. The ventricular function was preserved until then. Considering these initial data, some considerations about the etiological diagnosis of the dyspnea must be made.

The low output, secondary to the bradycardia, could be the initial causal factor of the dyspnea and the heart pacemaker implant was well indicated, considering the findings of the electrophysiological study (worsening of the block during programmed atrial stimulation). The hypertrophic cardiomyopathy is another possible etiology of the symptoms presented by the patient. It is transmitted by dominant autosomal inheritance, characterized by asymmetric septal hypertrophy and can cause pressure gradient in the left ventricular outflow tract.
The increase in this gradient is generally associated to the worsening of symptoms and it is considered an independent predictor of the heart failure syndrome progression and mortality. Effort dyspnea is the most common symptom, affecting more than 90% of the patients. It can result from a variety of mechanisms: diastolic dysfunction secondary to myocardial hypertrophy, ventricular emptying hindrance secondary to obstruction, mitral regurgitation and less commonly to the systolic function.

The initial distinction of the athlete’s heart is subtle, when there are smaller degrees of septal hypertrophy, as in the present case. Athletes usually have a symmetric hypertrophy and of ventricular thickness of around 12 mm, which can, in extreme cases, reach 14 to 16 mm. Other common diseases, such as systemic arterial hypertension and aortic valvular stenosis can course with similar symptomatology; however, these entities were ruled out by the absence of clinical and laboratory findings. Rarer pathologies, such as sarcoidosis, amyloidosis and Fabry’s disease are part of the differential diagnosis of the present case.

Systemic inflammatory disease such as sarcoidosis can affect the heart in 5% of the affected individuals, although autopsies have shown a subclinical involvement of up to 20 to 30% of the patients. First-degree atrioventricular blocks due to disorders in the atrioventricular node of HIS bundle and several degrees of intraventricular blocks are common among patients with sarcoidosis. These lesions can be initially silent, but can progress to a total atrioventricular block and cause syncope. Ventricular arrhythmias are the second most important cause of cardiac involvement in sarcoidosis. Its granulomas can be foci of automatism or re-entry, resulting in the onset of sustained or nonsustained ventricular tachycardias.

The diagnosis of sarcoidosis as cause of cardiomegaly and heart failure can be difficult, especially with no evidence of other organs being affected. Many of these patients can receive the diagnosis of idiopathic dilated myocardopathy; however, they present higher incidence of atrioventricular blocks, abnormalities of the ventricular wall thickness and segmental mobility, in addition to perfusion defects that affect preferentially the apical and anteroseptal regions. The diagnosis of cardiac involvement is attained through the endomyocardial biopsy with the finding of non-caseous granulomas associated to the characteristic clinical picture.

Amyloidosis is a systemic disease characterized by the extracellular deposition of microfibrils that can affect the heart, basically causing right heart failure, with left ventricular dysfunction manifestations being rare. In spite of the high degree of cardiac conduction system involvement seen at autopsies, high-degree blocks are uncommon.

An unusual presentation is the disproportional accumulation of amyloid material in the interventricular septum, mimicking hypertrophic myocardiopathy. The endomyocardial biopsy disclosed hyaline deposits of amorphous substance in the extracellular matrix, Congo-red positive, which turned into a green color at polarized light.

Fabry’s disease is a lysosomal disease characterized by the deposit of globotriaosylceramide in the lysosomes. It results in a multi-systemic disease that manifests as peripheral neuropathy, angiokeratomas, corneal deposits and renal failure. The cardiac involvement consists in concentric ventricular hypertrophy, heart failure, coronary disease and conduction disorders. Some patients present left ventricular hypertrophy as the only clinical manifestation of the disease.

After a few months of evolution, the patient courses with marked deterioration of the ventricular function and symptomatic ventricular tachycardias, relatively rare in patients with hypertrophic myocardiopathy and preserved

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Figure 5 - ECG - functioning double-chamber pacemaker stimulating atriums and ventricles.
ventricular function, although rather more frequent after ventricular dilation.

The evolution to ventricular dysfunction and decrease in the hypertrophy (as documented in later echocardiograms) can be found in a small number of the patients with hypertrophic myocardiopathy (5 to 15%) and it is currently the commonest cause of indication for heart transplant in these patients. It is more common in younger patients at presentation, those with more severe symptomatology, larger ventricular cavities and those with a family history of hypertrophic myocardiopathy with evolution to ventricular dilation.

The initial hypothesis that the pacemaker caused ventricular dyssynchrony and posterior dysfunction is based on several studies in which the delay in intraventricular conduction or left branch block were associated with a worsening of the symptoms and functional class, in relation to patients with normal intraventricular conduction.

Although the impact of dyssynchrony is higher in patients with established ventricular dysfunction, it has been demonstrated that the left branch block is associated with lower ejection fraction, when compared to healthy controls (54% vs. 62%) 

However, the present case’s evolution was characterized by a fast and marked ventricular dysfunction in a heart with a previous normal function. Additionally, in the specific population of patients with hypertrophic myocardiopathy, these hemodynamic effects induced by the stimulation of the right ventricle can be of clinical use in symptom improvement. The simulation through an electrode cable positioned at the extremity of the right ventricle modifies the sequence of ventricular activation, which changes from down to up and from the right to the left side. This fact results in the paradoxical movement of the interventricular septum, causing it to separate from the left ventricular posterior wall during the systole and resulting in:

1) increase in the diameter of the ventricular chamber;
2) decrease in the anterior movement of the anterior leaflet of the mitral valve and
3) decrease in the left ventricular outflow tract gradient.

These effects, however, did not translate into improvement in the maximum oxygen consumption (VO2 max) and of symptoms in randomized, double-blind studies, although they significantly decreased the left ventricular outflow tract gradient, thus currently making this therapy an exception.

The myocardial perfusion scintigraphy findings are compatible with microcirculation alterations or disease of the large epicardial vessels; however, the absence of risk factors for coronary artery disease and the previous year’s coronary angiography, make the first hypothesis the most probable one. These findings, however, confer a higher risk of future cardiovascular events to patients with hypertrophic myocardiopathy and perhaps, an increase in mortality.

The implant of the cardiodefibrillator associated to the atioventricular pacemaker was carried out based on several publications, which demonstrated symptom and survival improvement with the cardiac resynchronization of patients with severe dysfunction and electrocardiographic evidence of ventricular dyssynchrony, in spite of the optimized clinical treatment, to provide additional benefit to that of the secondary prophylaxis of poorly tolerated ventricular tachycardias previously presented by the patient.

There is limited evidence regarding drug therapy of the final phase of hypertrophic myocardiopathy, when there is evolution to ventricular dilation and systolic dysfunction. This patient received the treatment already established for systolic dysfunction in an attempt to decrease the morbitmortality: ACEI, beta-blocker, spironolactone, loop diuretics and amiodarone plus oral anticoagulant agent, due to the history of ventricular arrhythmia and the presence of thrombus in the left ventricle.

The capacity to exercise is decreased even at the initial phases of heart failure. The cardiac output might be normal at rest; however, it is incapable of increasing adequately, even during slight efforts. The maximum oxygen consumption (VO2) provides the most objective information regarding the functional capacity of patients with heart failure, and it is very important for the decision-making of when indicating the heart transplant.

Studies have shown that patients with a maximum VO2 < 10ml/Kg/min have a worse prognosis when compared to individuals with the same characteristics and higher functional capacity. Currently, the peak VO2 ≤ 14 ml/Kg/min is considered the cut-off for the indication of heart transplant in patients that present betablocker intolerance and 12 ml/Kg/min in the presence of this medication. Another possibility is the measurement of the ventilatory efficiency that corresponds to the ratio between ventilation per minute and CO2 production (VE / VCO2 slope), which is a much easier measurement to be obtained than maximum exercise capacity parameters and it is a better predictor of prognosis than the maximum VO2, NYHA functional class or LVEF. A VE / VCO2 slope > 35 is associated with decreased cardiac output during exercise, increase in the pulmonary artery occlusion pressure, decreased survival, and is a poor prognosis predictor in patients with preserved exercise capacity.

The endomyocardial biopsy has been increasingly used to help the etiological diagnosis of short-term evolution ventricular dysfunction. Heart failure with an evolution longer than three months, associated to ventricular dilation and new ventricular arrhythmias, second- or third-degree atrioventricular blocks or clinical therapy failure during treatment for more than 15 days is indicated with a level of evidence Ia. This procedure could help the diagnosis of the present case, as its evolution to dysfunction was very fast to be explained solely by dysfunction induced by pacemaker or by the natural evolution of hypertrophic myocardiopathy.

The patient was submitted to a bicaval orthotropic transplant and De Vega plastic procedure in the tricuspid valve. During the intraoperative period, he presented total atrioventricular block (TAVB), which required an epicardial pacemaker implant. Bradycardiac rhythms occur in more than 50% of receptors in the immediate postoperative period and are probably related to sinus node or atrioventricular node dysfunction. Its etiology might be related to rejection (studies show that the tissue of the conduction system is a frequent target of cell and humoral rejection), prolonged ischemia time, problems related to the surgical technique, coronary anatomy abnormalities or donor’s sinus dysfunction. Some studies correlate the occurrence of
bradyarrhythmias and the need for pacemaker after heart transplant to a worse prognosis43; however, these data have not been confirmed by other authors44.

After the first postoperative day, the patient presented a picture of hemodynamic and multiple organic function instability. The fifth-postoperative day echocardiogram showed biventricular dysfunction with LVEF of 35% and the patient died on the sixth postoperative day. One must consider the main causes of early graft failure after heart transplant, which are: hyperacute rejection, acute rejection (cell and humoral), prolonged donor’s ischemia time, reperfusion lesion and marginal donor.

The hyperacute rejection, which is rare nowadays due to the preoperative screening and cross-match carried out in sensitized individuals, is precipitated by the presence of preformed receptor’s antibodies that react against endothelial epitopes of the graft45. It is present in cases of ABO system incompatibility, but it can also be present in individuals that are highly sensitized (women with multiple pregnancies, patients submitted to multiple blood transfusions). It usually occurs within the first 24 hours after the transplant and can be observed as early as during the surgical procedure, leading to catastrophic graft failure.

The acute rejection is a common problem after heart transplants. It occurs particularly in the first month, generally by cell rejection46. Only 5% of the cases present severe hemodynamic involvement47. The majority does not present symptoms, which, when present, vary from unspecific pictures to classic ventricular dysfunction syndromes. The echocardiogram demonstrates the presence of the systolic or diastolic dysfunction and both ventricles can be involved. The diagnosis is established by endomyocardial biopsy, according to the ISHLT (International Society for Heart and Lung Transplantation) score, revised in 200548. A mononuclear, predominantly lymphocytic, inflammatory response can be observed, directed to the graft, with presence of damage to the myocytes. In severe cases, there is granulocyte participation. This is the main diagnostic hypothesis, considering the early clinical deterioration, although not in the first 24 hours, despite the lack of data about the immunosuppression regimen employed. The use of calcineurin inhibitors might have been avoided due to the onset of renal dysfunction with oliguria.

Some patients present a picture of hemodynamically significant rejection with little or no cell infiltrate or myocyte necrosis at the biopsy. These must present humoral rejection, associated to the deposition of antibodies that are detected at the immunofluorescence49. The humoral rejection can occur very early (2 to 7 days, usually in the first month post-transplant) and the graft dysfunction is severe in up to two-thirds of the early episodes, presenting hemodynamic involvement in up to 50% of them, which is rare in later episodes50,51.

Other important causes of early graft dysfunction that must be considered are: prolonged ischemia time, significant if > 4 hours, reperfusion lesion (which can be the cause of transient dysfunction) right ventricular dysfunction due to pulmonary hypertension (unlikely, considering the right catheterism of the patient) and causes related to the donor’s conditions, such as high doses of catecholamines, donor’s depressed systolic function, coronary artery disease, old age and previous surgeries52.

• Diagnostic hypothesis: more probable: cardiac sarcoidosis, or less probable: hypertrophic cardiomyopathy;
• Cause of death: hyperacute rejection.

Necropsy

This patient presented systemic sarcoidosis. The disease was diagnosed only at the anatomopathological assessment of the heart removed for cardiac transplant (Figures 6 and 7). It affected the following organs: thoracic lymph nodes, lungs (parenchyma and pleura), liver, spleen, and most importantly, the heart. In this case, it caused dilation of the four chambers caused by the extensive substitution of the right ventricle myocardium by areas of granulomatous inflammation and fibrosis. As it determined congestive heart failure, it led to the indication of an orthotopic heart transplant.

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Figure 6 - Macroscopic aspect of the heart, showing the open right ventricle, which is dilated, with extensive areas of fibrosis (green arrow: compare with area of preserved myocardium indicated by the blue arrow). V – Tricuspid valve.
After a good postoperative evolution for a few days, the patient presented a relatively fast worsening and died with biventricular dysfunction. The cause of the poor evolution was a mixed acute, humoral and cell rejection (Figures 8 and 9). The patient presented acute pulmonary edema—the final cause of death—in addition to a small pulmonary thromboembolism to the right, of which role, considering the degree of myocardial lesion, was secondary. There was also renal failure, which can be classified as pre-renal, due to the absence of significant pathological alterations in the kidneys.

Sarcoidosis is a rare disease, of which etiological factor is yet to be defined. The anatomopathological diagnosis is relatively easy, based on the finding of non-caseous granulomas and a negative result in the search for infectious agents. The involvement of the heart has been detected in 20% to 30% of autopsies of patients with sarcoidosis.

The present case is the second one at InCor in which the diagnosis of sarcoidosis was made in the explanted heart. The same has occurred in other Centers. Although the indication for transplant in known cases of the disease is controversial, due to possibility of recurrence, a comparative study has shown that the one-year survival is higher than in patients transplanted due to other causes.

In the last five years, there were 30 necropsies of adult patients at InCor that had been submitted to heart transplant. Eighteen of them died within 30 days of evolution. Among them, the most common cause of death was perioperative ischemia; there was rejection in 4 (22.2%), with two acute, this case, which was mixed, and a hyperacute one. Coagulopathy was responsible for the death in 2 patients (11.1%), right ventricular dysfunction due to pulmonary hypertension in 2 (11.1%) and other causes in the remaining patients. Mixed rejection, as in the present case, is the one that meets the anatomopathological criteria of both cell and vascular/humoral rejection.

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- **Anatomopathological Diagnosis:** cardiac and systemic sarcoidosis (explanted heart); mixed acute rejection, vascular/humoral and cell (transplanted heart)
- **Cause of death:** acute pulmonary edema

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References


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