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Original Research

TRANSPLANTATION

Mediastinal Lymphadenopathy in Patients Undergoing Cardiac Transplant Evaluation

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Background: **We evaluated the association between hemodynamic parameters of chronic congestive heart failure (CHF) and mediastinal lymphadenopathy (MLA) in heart transplantation (HT) candidates and the effect of HT on MLA. We also described the results of lymph node (LN) biopsies of MLA in the patients.**

Methods: **Patients who underwent HT evaluation over an 8-year period and had chest CT scans were evaluated retrospectively. Data collected included LN sizes pre-HT and post-HT, echocardiographic measurements, radionuclide-derived ejection fraction, and right-sided heart catheterization hemodynamics. MLA was defined as LNs > 1 cm in smallest dimension.**

Results: **Of 118 patients, 53 patients had MLA. MLA had weak statistically significant correlations with elevated mean pulmonary artery pressure (MPAP), mitral regurgitation (MR), tricuspid regurgitation (TR), right atrial pressure (RAP), and pulmonary capillary wedge pressure (PCWP). Thirty-six patients with MLA underwent HT, and nine of the 36 had post-HT chest CT scans. All nine patients showed a decrease in LN size post-HT (mean LN diameter pre-HT = 1.16 ± 0.137 cm, post-HT = 0.75 ± 0.32 cm). Seven of 53 patients with MLA underwent biopsies. Four had benign LNs, one had sarcoidosis, and two had lung cancer.**

Conclusions: **MPAP, MR, TR, RAP, and PCWP had weak statistically significant correlations with MLA. HT led to regression of MLA in patients who underwent CT scans post-HT, implying that MLA is related to CHF. However, we also identified clinically important causes of MLA; therefore, biopsy should be considered if enlarged LNs fail to regress after maximal medical management of CHF.**

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Abbreviations: CHF = congestive heart failure; CO = cardiac output; EBUS = endobronchial ultrasound; EF = ejection fraction; EUS = endoscopic ultrasound; HT = heart transplantation; LN = lymph node; MLA = mediastinal lymphadenopathy; MPAP = mean pulmonary artery pressure; MR = mitral regurgitation; MUGA = multigated acquisition scan; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RVG = radionuclide ventriculography; TR = tricuspid regurgitation

Mediastinal lymphadenopathy (MLA) is not commonly recognized as associated with congestive heart failure (CHF). However, recent case series have reported a 35% to 81% incidence of MLA in different patient populations with CHF.[1-4] However, the true incidence remains unknown as these reports analyzed different heart failure populations.

The lymphatic circulation is primarily responsible for regulating pulmonary fluid homeostasis. The lymphatic system is highly recruitable and, with time to adapt, can increase clearance of pulmonary edema fluid by > 10-fold. This system enables low-pressure drainage of excessive fluid from the interstitium through lymph nodes (LNs) and into collecting ducts. Lymphatic

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vessels are located in the connective tissue of the interlobular septa, the peribronchial sheath, and the pleura.[5] Fluid flows through the lymphatic system and drains into the venous circulation. Patients with CHF have chronically elevated left- and occasionally right-sided filling pressures leading to increased fluid clearance pathways (ie, the lymphatic system), which drain the lung parenchyma as a compensatory mechanism.[4] Therefore, it is plausible that mediastinal LNs might become enlarged from CHF when mediastinal edema related to critical pulmonary edema exceeds the clearance capacity of the lungs and pleura.[6]

MLA has been described in both acute and chronic CHF.[3,4] Patients with acute CHF have shown regression or resolution of lymphadenopathy after adequate pharmacotherapy.[7] However, one study of diuretics and additional pharmacotherapy for chronic CHF did not result in a decrease in the size of the mediastinal LNs.[4] These data suggest that the pathophysiologic mechanisms causing MLA are different in acute as compared with chronic CHF.

There are no standard criteria to establish CHF as the cause of MLA. Many patients with CHF may have risk factors for malignancy (ie, smoking history, age). Therefore, it is essential to secure a diagnosis of CHF-related MLA in heart transplantation (HT) candidates as recipients will require immunosuppression that could have catastrophic consequences in patients with concomitant infection or malignancy.[8]

We postulated that a cardiac transplant referral population was an appropriate group in which to evaluate chronic CHF-related MLA. Most of these patients undergo CT scans of the chest during their transplant evaluation. Because a subgroup of these patients underwent transplantation, it allowed us to evaluate their MLA before and after definitive therapy for CHF. Previous studies of CHF-related MLA evaluated patients before and after pharmacotherapy for CHF, which we suspect is not always effective.[1]

In this study, we retrospectively analyzed the presence and degree of MLA detected on chest CT scans in patients referred to our medical center for HT over an 8-year period. Furthermore, we correlated the degree of MLA with several measurements of ventricular performance. We also analyzed the effect of HT on mediastinal adenopathy. Finally, we report data concerning the subgroup of patients who underwent mediastinal LN biopsy for a clinical indication.

Materials and Methods

Study Design

The population was composed of patients with end-stage cardiomyopathy referred for cardiac transplantation at the Medical University of South Carolina from March 27, 1997, to November 15, 2005. Patients were excluded if they did not have a chest CT scan performed within 3 months of routine cardiac imaging and hemodynamic assessment as part of their transplant evaluation. Chest CT scans were ordered routinely in patients with a $\geq$20 pack-year smoking history and at the request of pulmonary consultants. The outcome variable for this study was the presence or absence of an abnormally enlarged mediastinal LN on chest CT scan. An enlarged mediastinal LN was defined as an LN $>$1 cm in the smallest dimension. Each CT scan of the chest was interpreted by a dedicated chest radiologist. Owing to the long period of time this study covered, CT scan technique was variable, encompassing helical scanners from single to 16 detector rows with slice thickness ranging from 1 to 5 mm depending on the study protocol. Although our standard protocol during the study period did not necessarily call for the use of IV contrast, the use of IV contrast was at the discretion of the radiologist, and its use during the study period was variable. Because IV contrast was not used in all cases, the measurements for hilar and interlobar LNs could not be accurately determined for all cases. The LN stations were recorded according to the American Thoracic Society criteria: 2R, 2L, 4R, 4L, 5, 6, 7, 8, and 9. Mediastinal LNs were measured in long and short axis.

Among patients who underwent transplantation and had a chest CT scan following transplantation, size comparisons were made between pre-transplant and posttransplant MLA. Measurements of LN sizes were performed with electronic calipers by a dedicated chest radiologist who was blinded in the posttransplant cases. Each posttransplant CT scan was read without prior knowledge of the location of enlarged LNs, and the largest LN was measured at each station.

Covariates in this study were measurements of ventricular performance and belonged to one of three classes: hemodynamic information, information derived from echocardiographic studies, and data derived from radionuclide ventriculograms (RVGs). Hemodynamic data were obtained from right-sided heart catheterizations performed by a cardiologist in the cardiac catheterization laboratory at the Medical University of South Carolina. Right internal jugular venous sheaths were placed under sterile conditions. Under fluoroscopic guidance, a pulmonary artery catheter was placed through the right-sided heart chambers, the pulmonary artery, and into the pulmonary capillary wedge position. The following hemodynamic measurements were assessed: right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), and pulmonary capillary wedge pressure (PCWP). Cardiac output (CO) was measured by thermodilution and assumed Fick methods.

Echocardiographic data were interpreted using standard American Society of Echocardiography criteria.[9] The measurements assessed included ejection fraction (EF) and mitral or tricuspid valvular insufficiency. Valvular insufficiency was graded on a scale of 0 to 3 corresponding to absent, mild, moderate, and severe, respectively.[10]

RVGs were also used to obtain an EF by using a technetium-99 standardized technique.[11] The RVG was performed with a γ camera equipped with a general, all-purpose, parallel hole collimator interfaced with a dedicated computer (Adac Argus Epic; Adac/Phillips Health Care; Andover, Massachusetts). The RVG-EF was determined from the left anterior oblique projection using semiautomated edge-detection algorithms, varying regions of interest throughout the cardiac cycle, and background correction. EF was calculated in the standard fashion: end-diastolic counts minus end-systolic counts/end-diastolic counts. Radionuclide studies were analyzed by physicians dedicated to the interpretation of nuclear medicine studies.

Demographic data collected included age, sex, race, and cause of heart failure. All testing was clinically indicated as part of each patient's pretransplant evaluation. The study was approved by the Medical University of South Carolina Institutional Review

Board for Human Research (committee 2, HR 19844), and it adhered to the tenets of the Declaration of Helsinki.

Statistical Analysis

The software used for these analyses were R version 2.10.1 (R Foundation for Statistical Computing; Vienna, Austria).[12] A frequency distribution of the abnormal LNs was constructed. Pearson product-moment correlation coefficients were calculated between all covariate measures and the number of abnormal LNs. Because multiple statistical tests were completed, we chose our level of significance (α) to be 0.0056 (Bonferroni method). Our institutional review board approved this study.

Results

Over the 8-year study period, we identified 118 cardiac transplant candidates who met our criteria for analysis. The mean age was 51.6 ± 9.5 years. Ninety-five patients (81%) were men, and 85 patients (72%) were white. The overwhelming majority of these patients had either an ischemic or idiopathic cardiomyopathy (Table 1). The mean time between chest CT scan and right-sided heart catheterization was 9 days (± 19 days).

Of the 118 patients studied, 53 (45%) patients had enlarged mediastinal LNs. The majority of patients with mediastinal LN enlargement had only one or two LNs that were enlarged. There were only two LNs with smallest dimension > 2 cm. No LN exceeded 3 cm in its smallest dimension (Fig 1). Data regarding number of enlarged mediastinal LNs, hemodynamics, echocardiographic findings, and EF by multigated acquisition scan (MUGA) are listed in Table 2.

There was a weak statistically significant correlation ($r = 0.28$, $P = .002$) between LN size and MPAP, between LN size and PCWP ($r = 0.22$, $P = .017$), and between LN size and RAP ($r = 0.23$, $P = .013$). Additional weak correlations were found between LN size and the presence of mitral regurgitation (MR) and tricuspid regurgitation (TR) ($r = 0.27$, $P = .003$; $r = 0.31$, $P = .007$, respectively). The other cardiac variables, including CO, cardiac index, echocardiogram EF, and MUGA EF, were not statistically significantly correlated with LN size (Table 3).

Table 1—*Causes of CHF by Percentage*

Cause	% (No.) (N = 118)
Ischemic cardiomyopathy	53 (63)
Idiopathic dilated cardiomyopathy	34 (40)
Alcohol-related cardiomyopathy	3 (3)
Failed Fontan surgery	2 (2)
Valvular heart disease	2 (2)
Sarcoidosis	2 (2)
Viral cardiomyopathy	2 (2)
Restrictive cardiomyopathy	1 (1)
Arrhythmogenic right ventricular dysplasia	1 (1)
Hypertrophic obstructive cardiomyopathy	1 (1)
Severe right-sided heart failure	1 (1)

CHF = congestive heart failure.

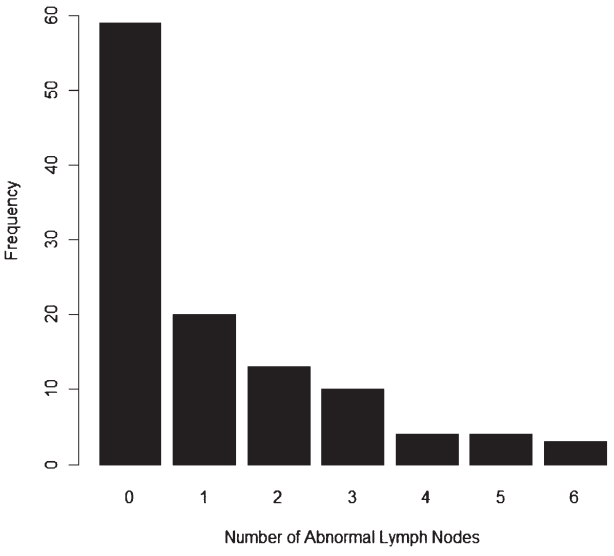

Figure 1. The percentage of patients with different numbers of enlarged mediastinal lymph nodes.

Of patients with MLA, 36 underwent cardiac transplantation. Of those transplanted, nine (25%) had a follow-up chest CT scan after transplantation, and all nine of these patients had regression in size of their MLA ($P = .01$). The mean LN diameter pre-HT was 1.16 cm ± 0.137 and post-HT was 0.75 cm ± 0.32.

Seven of the 118 total patients underwent diagnostic procedures (mediastinoscopy, endoscopic ultrasound [EUS], or endobronchial ultrasound [EBUS]-guided needle aspiration) either before or after cardiac transplantation to evaluate MLA observed on CT scan. The diagnosis varied among these patients as shown in Table 4. In three of these seven patients, distinct clinical symptoms or radiographic findings not easily attributable to CHF prompted biopsy of enlarged mediastinal LNs. The size of these LNs was greater in smallest dimension (mean, 1.7 cm; SD = 0.71) and in largest dimension (mean, 2.3 cm; SD = 1.9) than the mean size of LNs in the other patients with enlarged LNs. Of two patients in whom lung cancer was diagnosed, one patient underwent biopsy and cancer was diagnosed pretransplant because of cough, smoking history, and weight loss. The other patient developed lung cancer following transplant. This patient's LN biopsy specimens were negative for malignancy before transplant, and the cancer was found in a separate lung location 4.5 years after the transplant. Therefore, it was not believed to be a false-negative LN biopsy but rather a cancer that developed later after transplant (Table 4).

Table 2—*LN, Hemodynamic, Echocardiogram, and MUGA Data*

Variable	Mean	SD	Quartile			Minimum	Maximum	Missing
			First	Median	Third			
Nodes, cm	1.1	1.5	0.0	0.0	2.0	0.0	6	0
Hemodynamics								
RAP, mm Hg	9.3	7.4	4.0	8.0	12.5	0.0	48.0	10
MPAP, mm Hg	30.7	11.6	22.0	31.0	38.0	9.0	67.0	2
PCWP, mm Hg	19.6	9.4	13.0	21.0	25.0	1.0	40.0	8
CO, L/min	4.4	1.3	3.5	4.2	5.2	1.8	9.1	9
Cardiac index, L/min/m^2	2.2	0.7	1.8	2.2	2.4	1.0	5.2	9
Echocardiography								
EF	0.26	0.08	0.20	0.23	0.30	0.13	0.6	6
MR	1.1	1.0	0.0	1.0	2.0	0.0	3.0	2
TR	0.6	0.1	0.0	0.0	1.0	0.0	3.0	2
MUGA								
EF	0.22	0.11	0.14	0.21	0.28	0.04	0.7	8

CO = cardiac output; EF = ejection fraction; LN = lymph node; MPAP = mean pulmonary artery pressure; MR = mitral regurgitation; MUGA = multigated acquisition scan; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; TR = tricuspid regurgitation.

Discussion

The important findings of this study include the following: The frequency of MLA was 45% in this population of HT candidates. Of the hemodynamic parameters evaluated, an elevated MPAP, the presence of MR, the presence of TR, an elevated RAP, and an elevated PCWP had weak but significant correlations with mediastinal LN enlargement. In the group of nine patients transplanted with MLA, all nine had regression in the size of the lymphadenopathy after transplant. There were seven HT candidates (two of whom underwent transplantation) who had biopsies of enlarged LNs. Four of these patients had benign LNs, two had lung cancer, and one had sarcoidosis.

Previous case series found MLA in 35% to 81% of patients with CHF. However, these studies analyzed different patient populations. Higher percentages of MLA were typically observed in populations with acute CHF.[1-4] Lewin et al[4] evaluated mediastinal LNs detected by CT scan in a similar HT candidate population and found that 25 of 71 patients (35%) had MLA (at least one node >1 cm in shortest diameter). As in our study, they showed modest LN enlargement generally in the 1- to 2-cm range in smallest dimension. Lewin et al[4] did not reevaluate any patients following cardiac transplantation to look for regression in size. Lymph node biopsies were performed on only three patients with only benign results attained.[4]

Table 3—*Correlation With Abnormal Mediastinal LNs*

Variable	Correlation (*P* Value)
Hemodynamics	
RAP	0.23 (.013)
MPAP	0.28 (.0022)
PCWP	0.22 (.017)
CO	0.04 (.67)
Cardiac index	0.00 (1.0)
Echocardiography	
EF	0.05 (.59)
MR	0.27 (.003)
TR	0.31 (.0007)
MUGA	
EF	−0.17 (.067)

See Table 2 legend for expansion of abbreviations.

Some patients with chronic CHF adapt to very high PCWP and may not form pulmonary edema. It is conceivable that some may not develop CHF-related lymphadenopathy through similar compensatory changes. Normally, pulmonary edema occurs when fluid flows across the microvascular barrier of the lungs. Ernest Starling first described this occurrence as capillary hydrostatic force exceeding interstitial oncotic pressure.[13] Subsequently, it has been shown that hydrostatic forces favor transudation of fluid into the lungs to some degree, but there are mechanisms to counteract pulmonary edema. These mechanisms include alveolar barrier properties, such as lowered permeability of the epithelial barrier; the effect of surfactant, which lowers alveolar surface tension; and active transport by alveolar epithelial cells. Electron micrograph findings of thickening of the capillary endothelial and alveolar epithelial cell basement membranes in lung tissue specimens resected at the time of mitral valve surgery support the existence of mechanisms that prevent pulmonary edema. These specimens also showed that lymphatic vessels undergo compensatory changes including dilation and occasionally muscularization due to chronically increased edema clearance.[14-19]

Other mechanisms have also been proposed that are adaptive to increased hydrostatic pressure and prevent pulmonary edema.[20] It is probable that several of these mechanisms occur in different degrees

Table 4—*Diagnosis and Characteristics of LN Biopsies*

LN Biopsy Result	Follow-up Diagnosis	Patient Underwent Transplantation	Smallest Dimension of Largest LN, cm	Largest Dimension of Enlarged LNs, cm	Number of Enlarged LNs	Findings Leading to Biopsy
Normal LN	CHF	No	1.4	1.6	3	Dyspnea
Normal LN	CHF	No	2.2	3.3	6	Dyspnea
Normal LN	Lung cancer	No	3.2	3.7	4	Lung mass and weight loss
Noncaseating granulomas	Sarcoidosis	No	1.7	2.8	4	Lung nodule and dyspnea
Normal LN	Tuberculous empyema (2 mo after biopsy)	Yes (biopsy after transplant)	1.0	1.1	1	Dyspnea
Normal LN	CHF	No	1.4	2.8	4	Dyspnea
Normal LN	Lung cancer (55 mo after biopsy); LN biopsy considered a true negative	Yes (biopsy before transplant)	1.0	1.1	1	Dyspnea, lung mass 4.5 y after transplant led to lobectomy

See Table 1 and 2 legends for expansion of abbreviations.

in patients with CHF leading to varied clearance of edema through the lymphatics and therefore varying degrees of LN engorgement.

It was believed that the time (9 ± 19 days) between CT scans and right-sided heart catheterization was not excessive. The patient population did not include patients with acute exacerbations of CHF but rather included patients with chronic CHF on stable medical therapy.

Although previous case series of acute and subacute CHF have shown that elevated PCWP and low EFs were strongly associated with MLA,[1,2] our analysis in HT candidates only demonstrated weak but significant correlations between LN size and the following measurements of cardiac performance: (1) MPAP, (2) the presence of TR, (3) the presence of MR, (4) elevated RAP, and (5) elevated PCWP.

The explanation for the correlation between MLA and an elevated PCWP seems intuitive. An elevated PCWP is associated with fluid accumulation in the lung interstitium and alveoli. This fluid flux results from a capillary hydrostatic pressure increase secondary to elevated pulmonary venous pressure and left atrium venous return that exceeds left ventricular output. This fluid would be expected to fill the pulmonary lymphatic system and contribute to mediastinal LN enlargement. Similarly, MR may be expected to correlate with mediastinal LN enlargement as it typically leads to an elevated PCWP. The explanation of the correlation of MLA with RAP is more complex. An elevated RAP decreases pulmonary lymphatic drainage into the systemic venous circulation and lymphatic fluid causing fluid retention in the mediastinal lymphatics and LNs. Alternatively, in pulmonary venous hypertension secondary to left-sided heart failure, the PCWP leads to an elevated PAP, which can then lead to an elevated RAP, hence causing the correlation of RAP with enlarged mediastinal LNs.

MR and elevated MPAP may be related to an elevated PCWP, and may be directly or indirectly related to the presence of pulmonary hypertension. TR is also known to correlate with pulmonary hypertension and with RAP. It is notable that mediastinal and hilar lymphadenopathy have been reported in case series of pulmonary hypertension.[21] Additional support for the hypothesis that MLA in chronic CHF is the result of pulmonary hypertension is that chronic CHF can lead to pulmonary venous hypertension and that MR is a major determinant of pulmonary hypertension in patients with systolic heart failure.[22,23] In patients with chronic CHF and pulmonary hypertension, there may be more slowing of the lymphatic flow in the mediastinum due to chronically increased pressures in the systemic venous system. As pressure increases without increased lymphatic flow, LNs would be expected to become edematous. This would explain the finding that MLA was observed more frequently in patients with chronic CHF with pulmonary hypertension than in those without pulmonary hypertension.

This study showed that definitive therapy of chronic CHF (cardiac transplantation) led to a clinically significant resolution of MLA. In all nine patients who underwent cardiac transplantation and had MLA followed with serial chest CT scans, the lymphadenopathy regressed in size.

Previous studies have suggested that if mediastinal LN enlargement decreases with medical therapy for CHF, then further radiologic follow-up or tissue sampling is not necessary.[4] It may not be possible to take this diagnostic and therapeutic approach in the pretransplant population, because these patients often have a chronically elevated PCSP that is refractory to maximal medical therapy for CHF. Therefore, it may not be possible to lower filling pressures adequately to reduce lymphatic edema and lymphadenopathy.

HT candidates with MLA that does not regress with maximal medical management, especially those with LNs >2 cm in smallest dimension or unexplained symptoms such as weight loss, should undergo tissue confirmation of benign nodes prior to transplantation to ensure that infection or malignancy are not present. By performance of such LN biopsies, we did identify alternative causes of MLA in our cohort that had clinical implications (sarcoidosis and lung cancer). The authors are unaware of any direct evidence for the usefulness of PET scans in the diagnosis of lymphadenopathy related to CHF. PET scan was not part of the evaluation of lymphadenopathy in this study. Because lymphadenopathy related to CHF is not expected to be metabolically active, PET scan is likely to show low-grade or no activity above background.

Limitations

One limitation of this investigation is that it was retrospective. However, we did analyze data from consecutive patients who met entry criteria for this analysis. In addition, we did not perform chest CT scans routinely in HT recipients. There may have been a selection bias in those who received post-HT chest CT scans because these were only performed for a clinical indication.

Both the subgroup of patients who underwent cardiac transplantation and the subgroup who underwent LN biopsies were small. LN biopsies were not routinely performed in all patients with MLA after transplantation. However, all posttransplant chest CT scans of patients with pretransplant LN enlargement showed regression of the lymphadenopathy, suggesting that CHF-related lymphadenopathy was the correct diagnosis.

Measurements of regression in enlarged LNs following transplant were subject to interobserver and intraobserver variability as with most measurements, and differences in slice selection could account for minor changes in LN size measurements. These differences were not believed to impact the >50% reduction in size that was noted.

Future Directions

With the advent of transbronchial needle aspiration sampling via EBUS and EUS, assessment of the mediastinum is now accurate and less invasive than surgical assessment. Given the potential implications of failure to recognize an infectious or malignant cause of mediastinal adenopathy pretransplant, a prospective trial of sampling all enlarged mediastinal LNs in cardiac transplant candidates using EBUS and EUS should be considered. Because of the small number of patients undergoing biopsy in our study, we were unable to identify clinical criteria to ensure that MLA was the result of CHF pretransplant so that LN biopsy could be avoided.

As CT and PET scans cannot reliably exclude malignancy in LNs, recent research on other minimally invasive ways of predicting malignancy have stirred interest. The sonographic features of mediastinal LNs seen via EBUS have led to the search for a prediction model for malignancy that might eliminate the need for biopsies,[24] but more research in this area will be necessary.

In summary, our results support a relationship between CHF and MLA. The presence of MR, TR, elevated MPAP, elevated PCWP, and elevated RAP had a statistically significant but weak correlation with MLA, possibly as a result of cardiogenic pulmonary edema causing distention of the pulmonary lymphatics and also via pulmonary venous hypertension from chronic CHF. These hemodynamic correlations were too weak to suggest that one of them was a "driving force" for the development of MLA. Our sample size was not large enough to safely offer recommendations on LN characteristics that portend a specific pathologic diagnosis. In addition, it is known that imaging studies alone are unreliable as a means of diagnosing the cause of MLA. Presently, when cardiac transplant candidates are found to have mediastinal LN enlargement that does not regress with medical therapy, biopsy of these LNs is strongly recommended.

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Author contributions: *Dr Pastis:* contributed to the writing of the study protocol, acquiring data, wrote first draft of manuscript and reviewed all drafts, and has seen and approved the final version.
Dr Van Bakel: contributed to writing of the study protocol, data acquisition, reviewing all drafts of the manuscript, and has seen and approved the final version.
Mr Brand: contributed to writing of the study protocol and manuscript and data acquisition.
Dr Ravenel: contributed to data acquisition, reviewing all drafts of the manuscript, and has seen and approved the final version.
Mr Gilbert: contributed to data acquisition and the statistical analysis and reviewed the first draft of the manuscript.
Dr Silvestri: contributed to reviewing all drafts of the manuscript and has seen and approved the final version.
Dr Judson: contributed the initial concept for this study, contributed to writing the study protocol, reviewing all drafts, and has seen and approved the final version.
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