Giant Cell Myocarditis: Diagnosis and Treatment

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Abstract

Giant cell myocarditis is a rare but devastating disease that usually affects young otherwise healthy individuals. Associations with thymoma, inflammatory bowel disease, and a variety of autoimmune disorders have been reported. The rate of death or heart transplantation is approximately 70% at 1 year. Data from a Lewis rat model and from observational human studies suggest that giant cell myocarditis is mediated by T lymphocytes and may respond to treatment aimed at attenuating T cell function. Recent findings from the Giant Cell Myocarditis Registry, a clinical and pathologic database from 63 cases of giant cell myocarditis gathered from 36 medical centers, include the following: The sensitivity of endomyocardial biopsy for giant cell myocarditis for patients who undergo transplantation or autopsy is 82 to 85%. Registry subjects who received cyclosporine in combination with steroid, azathioprine, or muromonab-CD3 have prolonged transplant-free survival (12.6 months vs 3.0 months for no immunosuppression). Post-transplantation survival is approximately 71% at 5 years despite a 25% rate of giant cell infiltration in the donor heart. To confirm and extend these findings, a randomized trial of immunosuppression including muromonab-CD3, cyclosporine, and steroids is underway.

Key Words: Giant cell myocarditis · T-lymphocytes · Immunosuppression · Heart transplantation

Riesenzellmyokarditis: Diagnose und Behandlung

Zusammenfassung

Die Riesenzellmyokarditis ist eine seltene, aber schwere Krankheit, an der überwiegend junge, sonst gesunde Menschen erkranken. Es wurden Beziehungen zum Thymom, zu entzündlichen Darmerkrankungen und zu Autoimmunerkrankungen berichtet. Die Ein-Jahres-Mortalität oder Herztransplantationsrate beträgt 70%. Untersuchungen an einem Lewis-Rattenmodell und von Patienten deuten darauf hin, dass die Riesenzellmyokarditis durch T-Lymphozyten vermittelt wird und auf eine Behandlung, welche die T-Zell-Funktion vermindert, ansprechen könnte. Neuere Untersuchungen im Rahmen des „Giant Cell Myocarditis Registry", einem klinischen und pathologischen Register mit 63 Fällen von Riesenzellmyokarditis aus 36 medizinischen Zentren, zeigten, dass die Sensitivität einer Endomyokardbiopsie bezüglich Herztransplantation oder Autopsie 82 bis 85% beträgt. Patienten, die Cyclosporin in Kombination mit Steroiden, Azathioprin oder Muromonab-CD3 erhielten, wiesen ein verlängertes transplantatfreies Überleben (12,6 gegenüber 3,0 Monate) auf. Das Überleben nach einer Herztransplantation beträgt nach fünf Jahren 71%, obwohl es bei 25% zu einer Riesenzellinfiltration in das Donorherz kommt. Um diese Befunde zu bestätigen und zu erweitern, läuft zur Zeit eine randomisierte Studie mit immunsuppressiven Substanzen wie Muromonab-CD3, Cyclosporin und Steroiden.

Schlüsselwörter: Riesenzellmyokarditis · T-Lymphozyten · Immunsuppression · Herztransplantation

Giant cell myocarditis is a rare and usually fatal disorder that generally affects young otherwise healthy individuals. From 1905 until 1987 all cases were described at autopsy. The prognosis of giant cell myocarditis was grim with survival generally less than 3 months from symptom onset. Since 1987 several reports describe prolonged transplant-free survival of patients diagnosed by endomyocardial biopsy, usually in association with immunosuppressive treatment. This paper reviews the natural history, diagnostic strategies and treatment options for giant cell myocarditis. The histopathology and clinical course are compared to the related disorders of cardiac sarcoidosis and lymphocytic myocarditis.

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In the first half of the 20th century, the term "giant cell myocarditis" was used by various authors to describe both granulomatous and diffuse inflammatory myocardial infiltrates that contained multinucleated giant cells [37, 39, 71, 72]. Sarcoidosis in particular was well known to affect the heart and produce granulomatous lesions [36, 75]. Tesluk [79] first distinguished the well organized, granulomatous lesions of cardiac sarcoidosis from a diffuse, non-granulomatous infiltrate, which he called "giant cell myocarditis". Most authorities since have considered giant cell myocarditis a distinct clinical and pathological entity rather than a virulent form of isolated cardiac sarcoidosis [17, 55, 84].

Giant cell myocarditis is a pathologic diagnosis (Figures 1a and 1b). The criteria are a diffuse or multifocal inflammatory infiltrate consisting of lymphocytes admixed with eosinophiles and multinucleated giant cells. Myocyte damage must be evident in association with the inflammatory lesion [3, 12]. Varying degrees of fibrosis may be present [55]. Poorly formed granulomas may be seen in giant cell myocarditis, but well-organized follicular granulomas containing central giant cells exclude the diagnosis by definition. The lesions of active lymphocytic myocarditis may occasionally contain an isolated giant cell; nonetheless, giant cell myocarditis can usually be distinguished from lymphocytic myocarditis and granulomatous myocarditis even on biopsy specimens (Table 1).

The differential diagnosis includes a variety of infectious and systemic granulomatous diseases (Table 2). Ashoff lesions of rheumatic myocarditis evolve into characteristic, focal, interstitial granulomas with giant cells [3]. Tuberculosis and cryptococcus may also have giant cells within granulomatous lesions [20, 38, 73]. Special stains for organisms should be performed whenever there is a question of infection. Giant cell myocarditis has been described in a case of measles myocarditis [22]. Rarely giant cells may be seen in syphilitic myocarditis [73]. Foreign body reaction, Wegener's granulomatosis [54, 58], and systemic sarcoidosis must be considered in the differential diagnosis as well. These disorders have distinct clinical presentations and appropriate diagnostic studies usually preclude confusion with idiopathic giant cell myocarditis.

Up to 20% of giant cell myocarditis cases occur in individuals with other inflammatory or autoimmune disorders, especially inflammatory bowel disease (Table 3) [1, 7, 18, 42, 43, 59, 83]. Interestingly, a small percentage of patients who present with giant cell myocarditis at autopsy or explantation have clinically unrecognized granulomatous inflammation in other organs, including the aorta, lungs, liver, and lymph nodes [65]. These cases suggest that giant cell myocarditis can be the prime manifestation of a systemic granulomatous process. Therefore, the diagnosis of sarcoidosis or granulomatous infiltration in other organs does not always exclude giant cell myocarditis [17, 21].

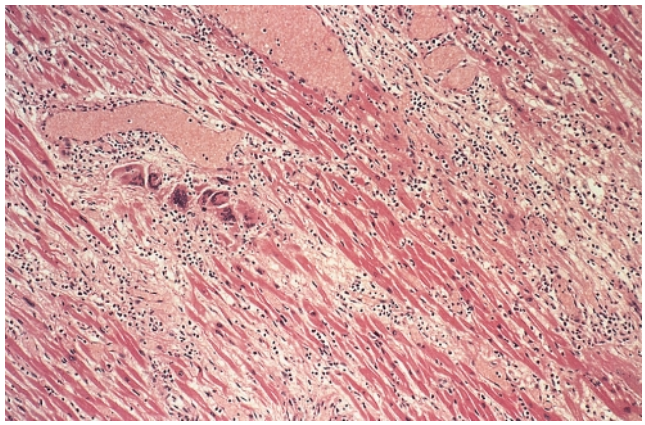

Figure 1a – Abbildung 1a

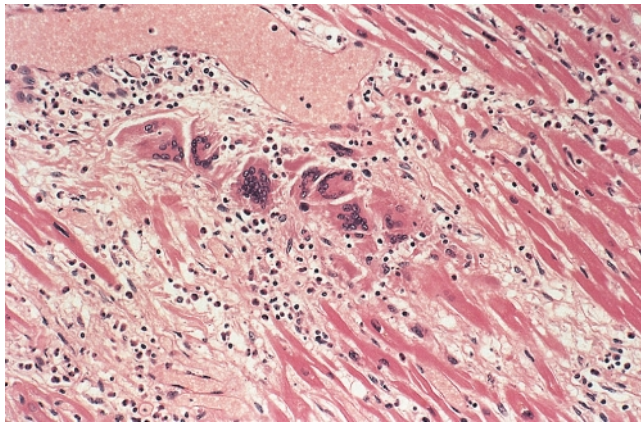

Figure 1b – Abbildung 1b

Figures 1a and 1b
a) Idiopathic giant cell myocarditis. A serpiginous inflammatory infiltrate with mononuclear cells, eosinophiles, and multinucleated giant cells. Myocyte destruction is seen in association with the inflammation. b) A cluster of multinucleated giant cells at higher power.

Abbildungen 1a und 1b
a) Idiopatische Riesenzellmyokarditis. Ein kriechendes entzündliches Infiltrat mit mononukleären Zellen, Eosinophilen und vielkernigen Riesenzellen. Die Zerstörung von Muskelzellen ist mit der Entzündung assoziiert. b) Eine Ansammlung von vielkernigen Riesenzellen.

Diagnosis	Definition	Gross pathology	Microscopic pathology	Comments
Giant cell myocarditis[1]	Widespread or serpiginous inflammation with myocyte necrosis in the absence of well formed granulomas or specific etiology	Pale, flabby myocardium. Dilation or hypertrophy may be present. Treated cases may have extensive scar	Widespread or serpiginous inflammation with giant cells, lymphocytes and often eosinophiles. Myocyte necrosis always present. Poorly formed granulomas may be seen	See Tables 2,3 and text for differential diagnosis and associated disorders
Cardiac sarcoidosis[2]	Granulomatous myocarditis with no evidence of infectious or other specific cause	Sharply defined areas of granulomatous inflammation or scar. Preferential involvement of papillary muscles, septum, and base of ventricles	Non-necrotizing granulomas, fibrosis with few eosinophiles. Myocyte necrosis is rare	Look for other organ involvement, anergy to common antigens, and ACE level to support diagnosis. Exclude fungi, mycobacteria, and foreign body reaction with special studies
Lymphocytic or idiopathic myocarditis[3]	A predominantly lymphocytic infiltrate with associated myocyte damage in the absence of acute infarction	Focal or diffuse inflammatory lesions	First pathology specimen may be active or borderline myocarditis, the latter having no myocyte damage. Subsequent samples may be persistent, healing, or healed per "Dallas criteria"	Associated with coxsackie B, adenoviral, and hepatitis C viral infections. Biopsy artifacts may resemble myocyte necrosis. Rule out many specific causes

[1]Cooper, et al. N Engl J Med 1997; Davies, et al. Br Heart J 1975; [2]Roberts, et al. Am J Med 1977; [3]Diagnostic Criteria for Cardiovascular Pathology, Bloom, ed. 1997; Aretz, Billingham, Edwards, et al. Myocarditis. Am J Cardiovasc Pathol 1986.

Table 1
Pathologic findings in giant cell myocarditis, cardiac sarcoidosis, and lymphocytic myocarditis.

Tabelle 1
Pathologische Befunde bei Riesenzellmyokarditis, kardialer Sarkoidose und lymphozytärer Infiltration.

The tumor most commonly associated with giant cell myocarditis is thymoma, particularly the spindle cell type [17]. Myasthenia gravis and myositis are associated with thymoma and giant cell myocarditis individually and in combination [4, 7, 8, 39, 42, 52, 60, 74, 81]. The association of thymoma with giant cell myocarditis occurs almost exclusively in women [41]. It has been postulated, but little evidence exists, that alterations in immune function associated with thymoma predispose to giant cell myocarditis [7]. Associations with sarcoma arising from the thymus [17] and lymphoma [29] have also been described; however, lymphoproliferative disease of the heart may be difficult to distinguish from giant cell myocarditis if myocyte necrosis is present.

The incidence of giant cell myocarditis is low and varies with the population studied. In a Japanese autopsy registry, the incidence of giant cell myocarditis was 0.007% (25 of 377,841 cases from 1958 to 1977) [63]. The incidence of giant cell myocarditis was a similarly low 3 of 12,815 necropsies from 1950 to 1963 at Oxford Infirmary [84]. In the early 1990s a selection of large, United States heart failure referral centers encountered a case of giant cell myocarditis (diagnosed by biopsy, apical wedge section, explanted heart or autopsy) about every 21 months (Giant Cell Myocarditis Registry, unpublished data).

Mechanism of Giant Cell Myocarditis

The cause of giant cell myocarditis is not known, but observations in human tissue and experimental data from a rat model suggest that the disease is mediated by T lymphocytes. Both human and experimental giant cell myocarditis are characterized by an infiltrate of T lymphocytes and histiocytes [45, 55]. In studies of human paraffin-embedded tissue, infiltrating lymphocytes are almost always positive for T cell antigens and giant cells are positive for macrophage antigens [1, 9, 10]. The T cell subsets (helper and suppressor ratios) may vary during the evolution of the infiltrate. Electron microscopy has failed to find viral particles or other clues to the etiology of giant cell myocarditis [10, 66, 82].

Experimental giant cell myocarditis can be produced in the Lewis rat by autoimmunization with myosin [47]. In this model, autoimmune giant cell myocarditis is characterized by CD4 positive T cells that produce interferon-gamma and macrophages that produce tumor necrosis factor (TNF) and nitric oxide (NO) [64]. The his-

Disorder	Associated findings and diagnostic studies	
Sarcoidosis	Granulomatous myocarditis without specific cause. Fibrosis may be prominent. Myocyte necrosis is rare.	Anergy to common antigens. Angiotensin converting enzyme (ACE) level. Look for other organ involvement.
Wegener's granulomatosis	Granulomatous myocarditis. Renal and upper and lower respiratory disease is generally present. Vasculitis may affect the coronary arteries.	C-ANCA, look for classic renal and respiratory findings.
Foreign body reaction	Giant cells may be associated with myocardial reaction to pacemaker leads or ventricular assist devices.	
Hypersensitivity myocarditis	Diffuse, primarily interstitial infiltrate with numerous eosinophiles. Myocyte necrosis and giant cells are infrequent.	Elevated liver function tests, eosinophil count, and skin rash.
Cardiac lymphoma	Hodgkin's disease rarely reported with myocardial granulomas with giant cells (Saphir O. Arch Pathol 1942)	Immunophenotyping. Look for extracardiac involvement.
Fungal myocarditis	Coccidiomycosis, blastomycosis, actinomycosis and others from granulomas. Seen in immunocompromised hosts, often with associated endocarditis or sepsis.	Special stains such as Grocott methenamine silver(GMS) and periodic acid Schiff(PAS) indicated.
Measles	Rare complication of measles. May cause myocyte necrosis and giant cell myocarditis.	Associated clinical findings.
Syphilis	Gumma may rarely involve the myocardium. Myocardial involvement is rarely isolated.	Associated clinical findings. VDRL.
Tuberculosis	Nodular, miliary, and diffuse infiltrative types. Myocardial involvement is rarely isolated.	Other organ involvement. PPD skin test.
Rheumatic carditis	Interstitial granulomatous infiltrate without myocyte necrosis in active lesion.	Jones criteria (Circulation 1965;32:664–8)

Table 2
Disorders that may resemble giant cell myocarditis.

Tabelle 2
Erkrankungen mit Riesenzellmyokarditis-ähnlichen Störungen.

tologic changes and hemodynamic deterioration are associated with inducible nitric oxide synthetase (iNOS) expression and attenuated by aminoguanidine, an inhibitor of iNOS [32]. In 2 models of autoimmune myocarditis (lymphocytic and giant cell), the disease can be transferred by T lymphocytes [44, 77].

Data from the rat model suggest that anti-T lymphocyte antibodies and cyclosporine, but not prednisolone alone prevent giant cell myocarditis [30, 46, 85]. Based on these observations, immunosuppression with muromonab-CD3 and cyclosporine would be a reasonable treatment for giant cell myocarditis. No published data exist for the use of other immunosuppressive agents such as immune globulin, cyclophosphamide, tacromlius, myophenolate (MMF), or anti-thymocyte globulin (ATG) for giant cell myocarditis.

Diagnostic Strategy

The diagnosis of giant cell myocarditis should be considered for all patients with subacute heart failure of unknown cause. Of the 63 Multicenter Giant Cell Myocarditis Registry cases [12], 75% present with congestive heart failure, 14% present with ventricular arrhythmia, and lesser percentages present with a syndrome mimicking acute myocardial infarction, heart block, or arterial embolization. The median time from symptom onset to presentation is 3 weeks. The median age is 42 years (range 15 to 69 years), but cases younger than 15 [25] and older than 70 [84] have rarely been reported. Men and women are affected equally, and cases have been described in many ethnic groups.

Common causes for heart failure and arrhythmia ought to be excluded per standard clinical practice. After a complete history, physical examination, electrocardiogram, and chest radiograph, an echocardiogram is usually obtained to exclude valvular and pericardial disease and cardiac masses. There are no specific echocardiographic findings to distinguish giant cell myocarditis from other forms of myocarditis; although, the rapid decline in ejection fraction that may occur over several

Inflammatory disorders
Ulcerative colitis [1, 59]
Crohn's disease [12]
Orbital and skeletal myositis [52]
Myasthenia gravis [7, 41]
Thyroiditis [2, 17, 34]
Takayasu's arteritis [40, 69]
Rheumatoid arthritis [70]
Pernicious anemia [43]
Alopecia totalis vitiligo [80]
Tumors
Thymoma [24, 41]
Lung carcinoma [2]
Lymphoma [29, 31]
Sarcoma [17]
Hypersensitivity reaction
Silicone rubber [49]
Anti-seizure medication [35]
Miscellaneous
Post-mitral valve surgery [67]
Mitral stenosis-associated [23]

Table 3
Disorders associated with idiopathic giant cell myocarditis.

Tabelle 3
Erkrankungen, die mit einer Riesenzellmyokarditis assoziiert sind.

days in giant cell myocarditis patients is uncommon in lymphocytic myocarditis or cardiac sarcoidosis. Coronary angiography is superior to non-invasive stress imaging to exclude significant coronary stenosis or dissection. Magnetic resonance imaging or computed tomography may be obtained if clinically indicated to help exclude such disorders as arrhythmogenic right ventricular dysplasia or constrictive pericarditis.

Endomyocardial biopsy ought to be considered for patients with heart failure or ventricular arrhythmia of less than 3 months duration who fail to improve despite optimal medical care. In most cases of lymphocytic myocarditis, the left ventricular ejection fraction will improve with usual care [57], whereas, the ejection fraction in giant cell myocarditis rarely improves [16]. The development of ventricular tachycardia or heart block further increases the likelihood of giant cell myocarditis [11, 12, 16]. The presence of associated disorders such as thymoma, myasthenia gravis, myositis, or inflammatory bowel disease (see Table 3) may provide valuable clues as well.

Because giant cell myocarditis usually affects the endocardium [55], right ventricular endomyocardial biopsy may have a high sensitivity. In a substudy analysis of Giant Cell Myocarditis Registry subjects, Shields et al. [76] found that endomyocardial biopsy had 82 to 85% sensitivity for giant cell myocarditis compared to the gold standard of surgical pathology (autopsy, explanted heart, or apical wedge section). This compares favorably to the roughly 35% sensitivity of endomyocardial biopsy in lymphocytic myocarditis, a more common but generally less severe and widespread process [61]. However, the Shields et al. study only included subjects who had both endomyocardial biopsy and surgical specimens, and therefore selected those with particularly poor prognosis. The sensitivity of endomyocardial biopsy would likely be lower in an unselected population of heart failure subjects with giant cell myocarditis.

Sampling error is a concern in endomyocardial biopsy, and a minimum of 5 and sometimes more specimens ought to be obtained. Occasionally, the diagnostic lesion will only be seen on additional cuts of the specimen blocks. Care must be taken to exclude hypersensitivity myocarditis, granulomatous myocarditis, foreign body reaction, and potential infectious causes using standard diagnostic criteria and appropriate special stains [3]. Once the diagnosis of giant cell myocarditis is certain, then one can consider the use of immunosuppressive agents in addition to usual care.

Other diagnostic techniques that have been suggested for viral myocarditis or cardiac sarcoidosis have not been applied to giant cell myocarditis. For example, antibodies to cardiac myosin have been described for patients with acute and chronic myocarditis [51]. Adenoviral and enteroviral DNA have been found in the hearts of patients with viral myocarditis [56]. Magnetic resonance imaging and newer echocardiographic techniques have been applied for myocarditis in pilot studies. Nuclear imaging with gallium-167 [33] to detect leukocytes or antimyosin antibodies to detect myocyte necrosis [61] has not been used to diagnose giant cell myocarditis. Because of the rarity and severity of giant cell myocarditis, a highly sensitive non-invasive test would be of great value; however, such a development is

unlikely without a much greater understanding of the cause of giant cell myocarditis.

Treatment of Giant Cell Myocarditis

Giant cell myocarditis is rapidly progressive and frequently requires the concurrent management of congestive heart failure, tachyarrhythmias, heart block, as well as secondary renal and hepatic insufficiency. Supportive care may include standard pharmacologic therapy of congestive heart failure, permanent or temporary pacemakers, implantable cardiac defibrillators (ICD) and intra-aortic balloon pump (IABP). The use of these drugs and devices should be dictated by standard clinical practice.

Ventricular assist devices (VAD's) are surgically implanted mechanical pumps that have been used to bridge patients with giant cell myocarditis to heart transplantation. Ventricular assist devices have been successfully used as a bridge to transplantation in patients with both lymphocytic [78] and non-specific myocarditis [68]. Brikalas et al. [6] reported a series of 9 patients from the Giant Cell Myocarditis Registry, who received ventricular assist devices. Successful bridging to transplantation in 7 of 9 (78%) is similar to that reported for other assist device recipients. Posttransplantation survival of 57% (4 of 7) at 30 days and 29% (2 of 7) at 1 year was unexpectedly low. Poor posttransplantation survival may have been due to poor pretransplantation condition of the patients. One patient with giant cell myocarditis has been successfully bridged to recovery with a biventricular Abiomed assist device (personal communication from patient).

Several case reports and the Giant Cell Myocarditis Registry suggest that treatment with certain combinations of immunosuppressants, but not steroids alone, prolong transplant-free survival [12, 15, 19, 53]. The median time to death or cardiac transplantation for all 63 Registry subjects is 5.5 months from onset of symptoms. 70% of affected individuals die or require heart transplantation within 1 year, and the overall rate of death or cardiac transplantation is 89% [12, 13]. Treatment with cyclosporine and steroid sometimes combined with azathioprine and/or muromonab-CD3 was associated with a median survival of 12.6 months compared to 3.0 months compared to those not treated with immunosuppressive agents ($p = 0.001$ by log rank test) [12].

These results must be interpreted very cautiously. The data stem from a small registry, not a randomized controlled trial. They are therefore subject to any number of uncontrolled factors that could possibly lead to an observed treatment effect substantially larger than the actual treatment effect. As an example, it's possible that the giant cell myocarditis patients in this registry with longer transplant-free survival times were more likely to receive combined immunosuppression therapy than the patients with shorter such times. If so, this would lead to a biased overestimate of the treatment effect.

The risks of aggressive immunosuppression in this setting are considerable. Cyclosporine can cause renal insufficiency, hypertension, liver function abnormalities, hirsutism, and gum enlargement. Muromonab-CD3 may cause profound hypotension, fever, chills, diarrhea, nausea, and vomiting. Long-term use of prednisone can cause osteoporosis and fractures, myopathy, cataracts and glaucoma. Therefore, these drugs should only be used to treat giant cell myocarditis by individuals experienced in their use at tertiary care centers.

Cardiac transplantation has been used with acceptable morbidity and mortality as a primary therapy for the management of giant cell myocarditis [5, 50, 62]. Enthusiasm for transplantation was tempered by several reports of posttransplantation giant cell myocarditis recurrence [26–28, 48]. The 39 Giant Cell Myocarditis Registry patients who underwent heart transplantation had a 71% 5-year survival, despite a 25% posttransplantation histologic recurrence rate on surveillance endomyocardial biopsies. Therefore, overall posttransplantation survival for giant cell myocarditis patients is comparable to survival for patients transplanted for cardiomyopathy [14].

The Giant Cell Myocarditis Treatment Trial

To control for possible bias in the Registry survival data and to investigate the mechanisms of giant cell myocarditis, the Multicenter Giant Cell Myocarditis Treatment Trial was organized. This study is a randomized, open-label trial of usual care plus muromonab-CD3, cyclosporine and steroids (prednisolone followed by prednisone) versus usual care without specified immunosuppression for giant cell myocarditis diagnosed by endomyocardial biopsy (endomyocardial biopsy). The primary efficacy endpoint is to compare the rate of death, transplantation, and ventricular assist device placement at 1 year (event-

free survival) in the 2 groups. To investigate the mechanism of survival benefit, hemodynamic and immunohistologic assessments will be obtained prior to treatment and during the study. The secondary efficacy endpoints include 1. the change in left ventricular ejection fraction measured by radionuclide angiography (RNEF), 2. the improvement in myocardial inflammatory infiltrate, and 3. functional status assessed by the Living with Heart Failure Questionnaire (LHFQ) before and after 4 weeks of treatment. Adverse events will be monitored and assessed by an independent safety monitoring committee.

Conclusions

The prognosis of giant cell myocarditis is poor, but prolonged transplant-free survival may be possible with aggressive immunosuppression if treatment is started within several months of symptom onset. Because of possible bias in the Giant Cell Myocarditis Registry survival data and the substantial risks of immunosuppression, the benefits of immunosuppression need to be confirmed in a prospective, randomized trial. Consider the diagnosis of giant cell myocarditis for patients with less than 3 months of progressive congestive heart failure or ventricular arrhythmia. Once the diagnosis is confirmed by endomyocardial biopsy, consider referral to a center involved in the Giant Cell Myocarditis Treatment Trial. Despite a substantial rate of posttransplantation giant cell infiltration on surveillance biopsies, the posttransplantation survival of giant cell myocarditis patients is comparable to posttransplantation survival for cardiomyopathy.

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