

Atrial Giant Cell Myocarditis A Distinctive Clinicopathologic Entity

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Background—Giant cell myocarditis (GCM) typically causes fulminant heart failure, arrhythmias, or heart block, necessitating aggressive immunosuppression, ventricular assist device insertion, or cardiac transplantation. We describe a novel variant of GCM, primarily involving the atria, that displays distinctive clinical features and follows a more benign course than ventricular GCM.

Methods and Results—We identified 6 patients (median age 67.5 years, 4 male) with atrial GCM in our pathology consultation practices from 2010 to 2012. Clinical history, imaging, and pathology materials were reviewed. Clinically, 4 patients had atrial fibrillation, 1 had acute heart failure, and 1 had incidental disease at autopsy. Among the 5 living patients, echocardiography revealed severe atrial dilatation (5 cases), mitral/tricuspid regurgitation (5), atrial mural thrombus (3), atrial wall thickening (2), and atrial hypokinesis (2). Ventricular function was preserved in all 5. Histological review of surgically resected atria showed giant cell and lymphocytic infiltrates, lymphocytic myocarditis-like foci, cardiomyocyte necrosis, and cardiomyocyte hypertrophy in all cases. Other features included interstitial fibrosis (5), poorly-formed granulomas (4), eosinophils (4), neutrophils (1), and vasculitis (1). Treatment consisted of steroids and cyclosporine (1), pacemaker placement for sick sinus syndrome (1), and supportive care (3). All 5 living patients returned to baseline exercise tolerance after 6 to 16 weeks of follow-up.

Conclusions—Atrial GCM represents a distinct clinicopathologic entity with a more favorable prognosis than classic ventricular GCM. This disorder should be included in the differential diagnosis of atrial dilatation, particularly when associated with atrial wall thickening. The utility of immunomodulatory therapy for this condition remains unknown. (*Circulation*. 2013;127:39-47.)

Key Words: heart enlargement ■ myocarditis ■ sarcoidosis

Idiopathic giant cell myocarditis (GCM) is a rare cardiac inflammatory disorder that is characterized by diffuse infiltration of the ventricular myocardium by lymphocytes and abundant multinucleated giant cells, frequent eosinophils, cardiomyocyte necrosis, and, eventually, fibrosis. Functional consequences of myocardial injury are similar to those seen in lymphocytic/viral myocarditis, including ventricular dysfunction and electrophysiological abnormalities, although these are usually much more severe in GCM.

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Most patients with GCM present with acute fulminant heart failure. Ventricular arrhythmias and heart block also occur commonly, and occasional cases may present with symptoms mimicking acute myocardial infarction.¹ The natural course is rapid and mortality is high if left untreated, with an average transplant-free survival of <6 months. Ventricular assist

device placements and immunosuppressive regimens, including high-dose steroids and cyclosporine, have modestly improved the prognosis in GCM, with an average transplant-free survival of >12 months. Nevertheless, many patients still eventually require heart transplantation.¹

GCM has been reported in association with autoimmune and neoplastic disorders, such as inflammatory bowel disease,^{2,3} systemic lupus erythematosus,⁴ Sjögren syndrome,⁵ myositis,⁶ and autoimmune hepatitis,⁴ as well as thymoma and myasthenia gravis.^{6,7} These support an autoimmune etiologic role, although autoantigens in GCM remain poorly defined. Animal studies indicate that a T lymphocyte-mediated immune response to anticardiac myosin antibodies may be involved,^{8,9} although these antibodies are not specific for GCM.¹⁰

Experimental evidence of a key role for T lymphocytes has provided rationale for using muromonab-CD3, a monoclonal antibody targeting T lymphocytes, as a treatment in combination with high-dose steroids and cyclosporine. Results of

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several case reports and trials of muromonab-CD3 therapy have been encouraging but variable.^{11–13} Despite improvement in treatment approaches, morbidity and mortality remain high.

GCM is a distinctly uncommon disorder. Even rarer are cases with atrium-predominant involvement. Atrial GCM (aGCM) was first described as a case report in 1964.¹⁴ After nearly a half-century, it still remains a poorly understood condition, and, to our knowledge, only 6 cases have been reported since that time.^{15–18} Herein we describe 6 additional cases of aGCM and characterize their clinical, radiological, and histopathologic features.

Methods

Six cases of aGCM have been identified in our pathology consultation practice at Mayo Clinic from 2010 to 2012. This study was approved by the Institutional Review Board. We reviewed pertinent aspects of the available clinical history for each case, including age, sex, underlying medical conditions (including autoimmune connective tissue disease, rheumatic heart disease, and sarcoidosis), cardiac history, surgical history, medication history, presenting symptoms, duration of symptoms, physical examination findings, laboratory results, electrocardiographic (ECG) findings, pulmonary function tests, and imaging findings, including chest radiographs, echocardiography, computed tomography (CT), angiography, and cardiac MRI.

Histology slides of cardiac resection or biopsy material from all cases were reviewed by 2 authors (B.T.L. and H.D.T.), and the original diagnoses were confirmed on sections stained with hematoxylin and eosin. The number of slides evaluated was tallied. Pertinent histological features and patterns were evaluated, including the presence of giant cells, poorly-formed granulomas, well-formed granulomas, cardiomyocyte necrosis, diffuse interstitial lymphocytic infiltrates, lymphocytic myocarditis-like foci (dense lymphoid aggregates intimately associated with cardiomyocyte necrosis), neutrophilic infiltrates, eosinophilic infiltrates, vasculitis, cardiomyocyte hypertrophy, and fibrosis. Each of these features was independently and semiquantitatively graded as 0 (absent), 1+ (focal, mild), 2+ (moderate), or 3+ (severe, diffuse).

Gomori methanamine silver and acid fast histochemical stains were performed in all cases. In some cases, immunohistochemical stains were performed using a commercial platform (Benchmark XT, Ventana Medical Systems, Tucson, AZ) and primary antibodies directed against CD3 (Ventana, titer 0.45 µg/mL), CD20 (Ventana, titer 0.3 µg/mL), and CD68 (Ventana, titer 0.4 µg/mL).

Details of the hospital course were recorded in each case, including operations performed, postoperative course, complications (if any), medications and devices used, and duration of hospitalization. Follow-up information was obtained, including current functional status, symptoms (if any), ECG findings, current medications, and results from follow-up imaging studies.

Results

Among the 6 cases of histologically-confirmed aGCM, all cases showed strong clinical or histological evidence of apparent isolation to the atrium with ventricular sparing. The median age was 67.5 years (range 42–73 years), and 4 patients were male. Clinical presentations varied, with 3 patients with chronic atrial fibrillation in whom aGCM was discovered at the time of elective maze/valve surgery, 1 patient with acute myocardial infarction and newly diagnosed atrial fibrillation in whom aGCM was discovered incidentally at the time of coronary artery bypass grafting, 1 patient with acute heart failure who underwent diagnostic atrial biopsies, and 1 asymptomatic patient with aGCM discovered incidentally at autopsy. Pertinent clinical details are summarized and compared with

previously reported cases in Table 1. Imaging findings, treatments, and outcomes are summarized in Table 2. Case histories are discussed in greater detail below.

Case 1

A 42-year-old man with a history of asthma, chronic obstructive pulmonary disease, and bipolar disorder, found deceased from unexplained causes, underwent postmortem examination. Grossly, both coronary artery disease and cardiomegaly were evident. Mild biventricular dilatation was noted, along with a small patent foramen ovale (0.4 cm potential diameter). The remainder of the gross examination was unrevealing.

Microscopic examination of the heart revealed findings consistent with GCM involving the right atrial (RA) appendage and RA free wall. Extensive additional sampling failed to demonstrate GCM in other areas of the heart, including the left atrium, atrial septum, ventricular septum, and ventricular free walls (both left and right), or a giant cell process in other thoracoabdominal viscera. Evidence of chronic ischemic heart disease was also identified, including interstitial fibrosis and cardiomyocyte hypertrophy in the left ventricle without plaque rupture or thrombosis of the coronary arteries.

Toxicological studies revealed critical serum concentrations of oxycodone, opioid metabolites, and benzodiazepines. Polysubstance overdose was listed as the cause of death. Isolated atrial GCM was regarded as an incidental finding that did not directly contribute to his death.

Case 2

A 58-year-old man with a history of hypertension and hyperlipidemia presented with progressive shortness of breath, exertional dyspnea, and chest pain. An ECG showed atrial flutter without evidence of myocardial ischemia. Echocardiography revealed severe dilatation and akinesis of the left atrium (LA), with mural thrombus, severe mitral stenosis, trace mitral regurgitation, and normal biventricular function with a left ventricular ejection fraction (LVEF) of 50% to 59%, suggesting rheumatic mitral valve disease. The patient underwent elective mitral valve replacement and a left atrial maze procedure.

Histological evaluation of the mitral valve revealed fibrosis and neovascularization without inflammatory infiltrates, consistent with chronic rheumatic mitral valve disease. The LA showed findings consistent with GCM. Treatment included anticoagulation, but immunomodulatory therapy was not used. His postoperative course was complicated by sick sinus syndrome, requiring pacemaker placement, but was otherwise uneventful. His symptoms resolved within 2 weeks, and he was discharged home.

Four months later, he remained asymptomatic. Follow-up echocardiography showed persistence of left atrial dilatation, a normal LVEF of 60% to 69%, and normal right ventricular function.

Case 3

A 65-year-old woman with a history of asthma presented with a 6-week history of progressive shortness of breath and exercise intolerance. She had no previous history of cardiac disease.

Table 1. Clinical Features of Atrial GCM at Presentation

Case #	Year (ref.)	Sex	Age (y)	Race	Symptoms	Symptom Duration	AF	Sarcoid	Rheumatic Valve Disease	Other Connective Tissue Disease	Other Past Medical History
1	2012*	M	42	W	None	n/a	Unk.	No	No	No	COPD, asthma, bipolar disorder
2	2012*	M	58	W	SOB, dyspnea, chest pain	Several weeks	Yes	No	Yes	No	HTN, HL
3	2012*	F	65	W	SOB, DOE, orthopnea, pedal edema	6 wk	Yes	No	No	No	Asthma
4	2012*	M	70	W	Chest pain	Several hours	Yes	No	No	No	HL, DM, CAD, MI
5	2012*	F	72	W	DOE, fatigue	Many years	Yes	No	Yes	No	HTN, HL, cerebral aneurysm
6	2012*	M	73	W	Fatigue, sudden left sided weakness	Several days	Yes	No	No	No	CAD, HTN, HL, DM, sleep apnea
7	2010 (18)	F	51	Unk.	CHF	Unk.	Yes	No	Yes	No	COPD, brachial artery thrombosis
8	2006 (17)	M	70	Unk.	CHF	Several years	Yes	No	No	Unk.	Unknown
9	1968 (16)	F	60	W	PND	9 y	Yes	No	Yes	Unk.	Popliteal artery embolism
10	1965 (15)	F	42	Unk.	CHF during pregnancy	1 y	Yes	No	Possibly	Unk.	Unknown
11	1965 (15)	F	54	Unk.	DOE	5 y	Yes	No	Possibly	Unk.	Unknown
12	1965 (15)	F	41	Unk.	DOE	3 y	Yes	No	Possibly	Unk.	Unknown
13	1964 (14)	M	37	Unk.	DOE, chest pain, myalgia	5 y	Yes	No	Yes	Unk.	Unknown

AF indicates atrial fibrillation/flutter; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DOE, dyspnea on exertion; GCM, giant cell myocarditis; HL, hyperlipidemia; HTN, hypertension; MI, myocardial infarction; n/a, not applicable; PND, paroxysmal nocturnal dyspnea; SOB, shortness of breath; Unk., unknown; and W, white race.

*Current cases.

Physical examination revealed elevated jugular venous pressure with prominent V waves, a soft pansystolic murmur at the left sternal border, a pulsatile liver edge, and mild pitting edema of the ankles, without other significant findings. Serum troponin I levels were within normal limits. CT angiography of the pulmonary vasculature did not demonstrate pulmonary emboli.

Pulmonary function tests revealed a forced expiratory volume at 1 minute that was 40% of predicted, forced vital capacity that was 68% of predicted, forced expiratory volume at 1 minute/forced vital capacity ratio of 46, carbon monoxide diffusing capacity that was 50% of predicted, and moderate to severe airflow obstruction.

ECG showed T-wave inversion in leads V_2 to V_6 . Transthoracic and transesophageal echocardiography showed marked biatrial wall thickening, RA dilatation, severe tricuspid regurgitation attributable to failure of leaflet coaptation, pulmonary artery pressures of 32 to 37 mm[Hg], and normal right ventricular and left ventricular size, without valvular vegetations. The LVEF was normal. Cardiac MRI confirmed these findings and also revealed tricuspid annular dilatation (Figure 1). T2-weighted imaging demonstrated marked myocardial edema that was isolated to the thickened atria.

The patient was referred for tricuspid valve repair and diagnostic biopsies of both atria, each of which showed histopathologic findings consistent with GCM. She then received a course of methylprednisolone (500 mg daily for 3 days) and was subsequently discharged on prednisolone (30 mg daily) and cyclosporine (75 mg twice daily). At a follow-up visit 8 weeks later, she reported a return to nearly normal exercise tolerance. Follow-up cardiac MRI showed dramatic

improvement with normal atrial wall thicknesses (Figure 2). One year later, her exercise tolerance remained normal with a gradual reduction in prednisolone and cyclosporine dosages, and she continued to do well.

Case 4

A 70-year-old man with a history of hyperlipidemia and diabetes mellitus presented to the emergency room with chest pain and was diagnosed with acute non-Q-wave myocardial infarction. ECG also showed atrial fibrillation, a new finding. He had no previous history of arrhythmia. On cardiac catheterization, he was found to have anterolateral akinesis with an estimated LVEF of 58% and severe multivessel coronary artery disease. Also present were severe LA dilatation, mild RA dilatation, moderate mitral regurgitation, and mild to moderate tricuspid regurgitation.

Two days later, the patient underwent coronary artery bypass grafting and a left atrial maze procedure, which included excision of a markedly thickened LA appendage. Histological evaluation of the resected LA appendage showed incidental findings consistent with florid GCM. Treatment was supportive and included anticoagulation therapy, and his hospital course was uneventful. At a follow-up visit 8 weeks later, he was asymptomatic, although he remained in atrial fibrillation.

Case 5

A 72-year-old woman with a history of chronic atrial fibrillation and severe mitral valve stenosis presented for elective mitral valve replacement and maze procedure because of progressively worsening exertional dyspnea and fatigue.

Table 2. Cardiac Clinical and Imaging Features, Treatment, and Outcome of Atrial GCM

Case # (ref.)	Valve Disease	Atrial Dilatation	Atrial Wall Thickening	Mural Thrombus	LVEF/LV Function	RV Function	Treatment	Duration of Course	Disease-Free Follow-Up
1*	None†	None†	None†	No†	Unknown	Unknown	n/a	n/a	n/a
2*	MS (severe), MR (mild)	LA (severe), with akinesis	Unknown	Yes	50% to 59%	Normal	Warfarin, pacemaker	2 wk	4 mo
3*	TR (severe), TV annular dilatation	RA (severe)	Yes (Bilateral, marked)	No	Normal	Normal	Steroids, cyclosporine	8 wk	12 mo
4*	MR (mod.), TR (mild-mod.)	LA (severe), RA (mild)	Yes (LAA)	No	58%	Normal	Warfarin	Unknown	8 wk
5*	MS (severe), MR (mild)	LA (severe)	Unknown	Yes	60% to 65%	Normal	Warfarin	2 wk	6 wk
6*	AR (trace), MR (mild), TR (mild)	LA (severe), with hypokinesis	Unknown	Yes	Normal	Normal	Warfarin	4 wk	8 wk
7 (18)	MS (severe), MR (mild)	LA (severe)	Yes (LAA)	Yes	Normal	Normal	Pacemaker	Unknown	2 y
8 (17)	MR (severe)	Biatrial (severe)	None	No	Normal	Normal	Pacemaker, amiodarone	Unknown	6 mo
9 (16)	MS, AR†	Biatrial (severe)†	None†	No†	Unknown	Unknown	Supportive	n/a§	n/a§
10 (15)	MS†	Unknown	Unknown	Yes	Normal	Normal	Unknown	Unknown	6 y
11 (15)	MS†	Unknown	Unknown	Yes	Normal	Normal	Unknown	Unknown	4 y
12 (15)	MS†	Unknown	Unknown	Yes	Normal	Normal	Unknown	Unknown	3 y
13 (14)	MS (mod.), MR (trace)†	LA	Unknown	Yes	Normal	Normal	Anticoag., digoxin	Unknown	8 mo

AR indicates aortic regurgitation; anticoag., anticoagulation; GCM, giant cell myocarditis; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; LVEF, left ventricular ejection fraction; mod., moderate; MR, mitral valve regurgitation; MS, mitral valve stenosis; n/a, not applicable; RA, right atrium; RV, right ventricle; TR, tricuspid valve regurgitation; and TV, tricuspid valve.

*Current cases.

†Autopsy findings (no imaging performed).

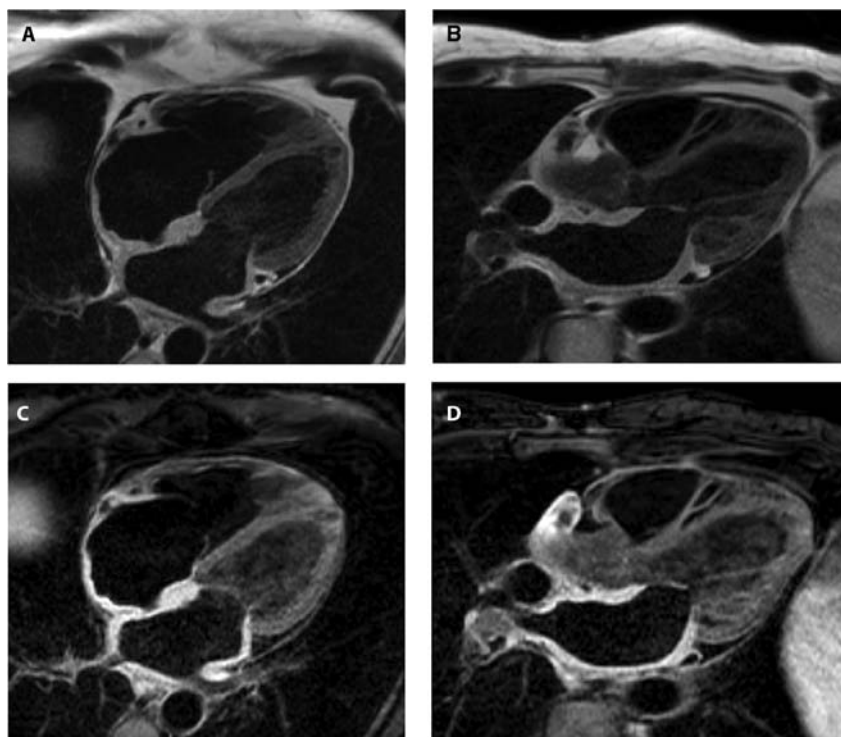
‡Clinical assessment (no imaging performed).

§Patient died in immediate postoperative period.

Echocardiography demonstrated severe LA dilatation with a large LA mural thrombus, in addition to severe mitral valve stenosis and a normal LVEF of 60% to 65%.

Histological evaluation of the surgically resected LA appendage revealed findings consistent with GCM. Treatment was supportive, and included anticoagulation therapy. Her

Figure 1. Cardiac MRI findings in atrial giant cell myocarditis. Representative MR images from Case 3 at the time of initial presentation. On T2-weighted imaging with end-diastolic 4-chamber (A) and 3-chamber (B) views, marked biatrial thickening and dilatation are readily apparent. T2-weighted spectral adiabatic inversion recovery (SPAIR) sequence imaging (C and D) shows marked edema of the atria, without ventricular involvement.



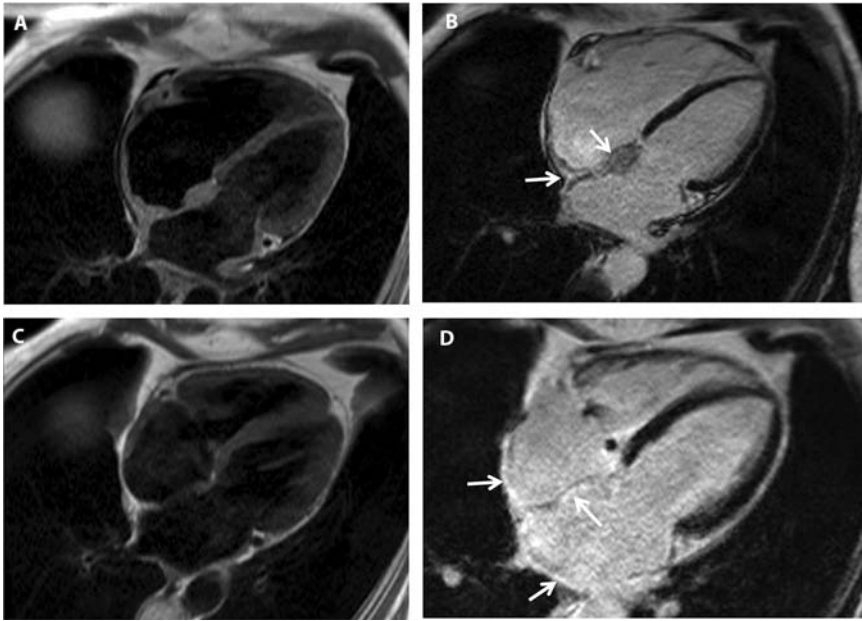


Figure 2. Effect of immunomodulatory therapy in atrial giant cell myocarditis. Comparison of cardiac MRI findings in Case 3 before (**A** and **B**) and 8 weeks after (**C** and **D**) treatment with high-dose corticosteroids and cyclosporine. On T1-weighted imaging, marked biatrial thickening at the time of initial presentation (**A**) is no longer present after treatment (**C**). Delayed gadolinium enhancement (arrows) in the atrial walls is seen at presentation (**B**), consistent with marked atrial inflammation, and is more pronounced after treatment (**D**), suggestive of extensive biatrial fibrosis.

postoperative course was complicated by a transient ischemic attack and respiratory failure on the first day, but these issues resolved and she was eventually discharged. At outpatient follow-up 6 weeks later, she reported resolution of dyspnea and fatigue, but remained in atrial fibrillation.

Case 6

A 73-year-old man with a history of coronary artery disease, chronic atrial fibrillation, and multiple previous cerebral transient ischemic attacks presented with complaints of generalized fatigue for several days and the sudden onset of left-sided weakness. Transesophageal echocardiography showed marked LA enlargement, low LA appendage flow velocities, a 2-cm filamentous excrescence on the aortic valve, trace aortic valve insufficiency, and preserved biventricular function.

The patient underwent resection of the aortic valve mass, which showed histopathologic findings indicative of an organizing thrombus. The RA appendage (removed to enable RA cannulation for cardiopulmonary bypass) showed histological findings consistent with GCM. Treatment was supportive, and included continuation of warfarin. Immunomodulatory therapy was not initiated.

Despite therapeutic anticoagulation, his postoperative period was complicated by multiple additional transient ischemic attacks over the ensuing weeks, but these eventually subsided and the patient was discharged home. At his outpatient follow-up evaluation 8 weeks from the time of initial presentation, the patient reported a return to baseline function. No permanent neurological deficits were identified. Follow-up echocardiography showed persistent atrial fibrillation, but biventricular function remained within normal limits.

Pathological Findings

Slides from all available heart tissue blocks were reviewed from each case (mean 5 blocks, range 1–21). Microscopic evaluation showed giant cells and interstitial lymphocytic inflammatory infiltrates, lymphocytic myocarditis-like foci,

cardiomyocyte necrosis, and cardiomyocyte hypertrophy in all cases (Figure 3). Other features included interstitial fibrosis (5 cases), poorly-formed granulomas (4), eosinophils (4), neutrophils (1), and vasculitis (1). Gomori methanamine silver and acid fast stains were performed in all cases, and no microorganisms were identified.

Immunohistochemical studies were performed in 3 cases, which documented the lymphocytic infiltrate in each case to be rich with CD3-reactive T lymphocytes, with fewer scattered CD20-reactive B lymphocytes, abundant associated CD68-reactive histiocytes and giant cells (Figure 4). This constellation of microscopic findings is the same as that seen in ventricular GCM (vGCM).^{19,20} Pathological findings are summarized in Table 3.

Discussion

To our knowledge, this represents the largest series of patients in a single report with atrial GCM. Although aGCM and vGCM show similar histopathologic features at the light microscopic level, they show markedly different clinical and radiological features. The distinctive, apparent absence of ventricular involvement in aGCM suggests that the pathogenesis of this disorder may differ substantially from that of vGCM. The natural course of aGCM also appears to be quite different from vGCM. Taken together, these features indicate that vGCM and aGCM are separate disease processes and that aGCM represents a distinct clinicopathologic entity.

Clinical Considerations

When GCM involves the ventricles, patients present with a constellation of clinical symptoms and signs that often suggest this diagnosis. However, as the present 6 cases (and those previously reported) illustrate, GCM occasionally involves the atria preferentially. This results in a different constellation of clinical and imaging findings, which may delay or hamper making the correct diagnosis, if clinicians are not aware of this

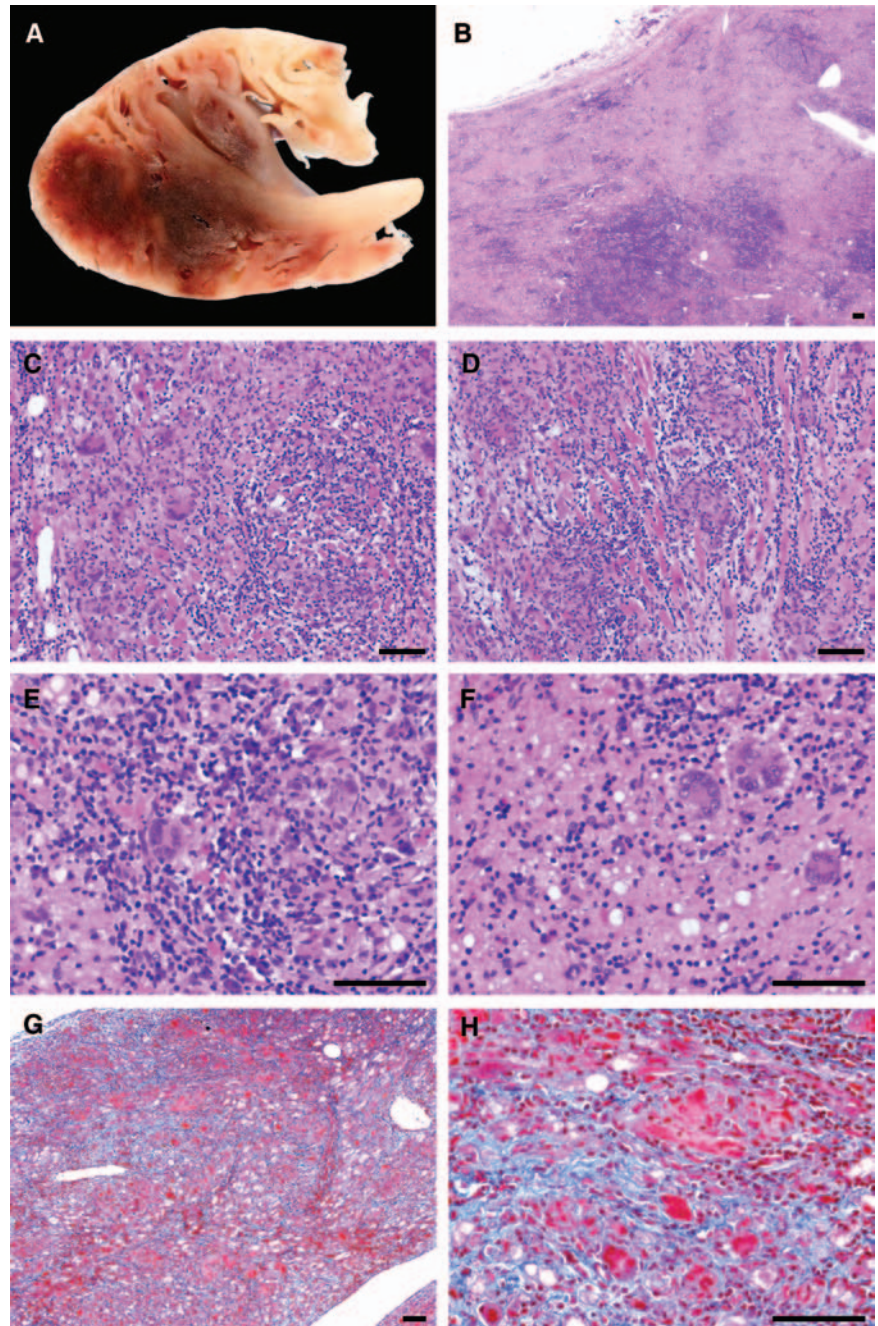


Figure 3. Histology of atrial giant cell myocarditis (GCM). **A**, Representative gross photograph of resected right atrial appendage from patient with atrial GCM. The atrial wall is diffusely thickened and inflamed. **B–H**, Representative photomicrographs of atrial myocardium from the same patient. **B**, A diffuse inflammatory infiltrate is readily apparent, even at low power. At medium power (**C**), numerous multinucleate giant cells are present in association with dense lymphocytic infiltrates, lymphocytic myocarditis-like foci, and cardiomyocyte necrosis, with (**D**) other areas showing scattered poorly formed non-necrotizing granulomas. At high power, the infiltrate is composed of (**E**) lymphocytes and plasma cells as well as (**F**) giant cells and scattered eosinophils. **G**, Extensive fibrosis (blue) replaces the atrial wall and is (**H**) intimately associated with areas of ongoing myocardial injury with giant cells. **B–F**, hematoxylin and eosin; **G–H**, Masson trichrome. Bars, 100 μ m.

entity. These findings include atrial fibrillation/flutter in nearly all cases, and severe atrial dilatation, mural thrombus, and mitral/tricuspid regurgitation in many cases. Atrial hypokinesis was identified in 2 cases and was probably an important factor in mural thrombus formation. Although atrial fibrillation seems to be a nearly universal finding in atrial GCM, the contribution of the inflammatory process to atrial arrhythmogenesis, if any, remains unknown.

An important limitation of most aGCM reports, including the present study, is the lack of direct histopathologic evidence of ventricular sparing from the inflammatory process and reliance on conventional clinical methods to diagnose an apparently atrium-limited disorder. Ventricular sparing in aGCM has been confirmed histologically in only 2 cases to date (Case

1 and a previously reported case¹⁶), and the possibility of ventricular involvement in other cases cannot be entirely ruled out. However, these 2 cases confirm that true atrial isolation of the giant cell myocarditic process occasionally occurs. In our remaining cases, clinical and imaging features indicate that ventricular function was preserved, suggesting that ventricular involvement, if any, was minimal and clinically insignificant, and that the inflammatory process may have also been isolated to the atria in these patients.

Without timely diagnosis and appropriate treatment of vGCM, the prognosis is poor and patients rapidly develop hemodynamic deterioration. Fortunately, the prognosis in aGCM appears to be much better than that observed in vGCM. The present case series shows that the clinical

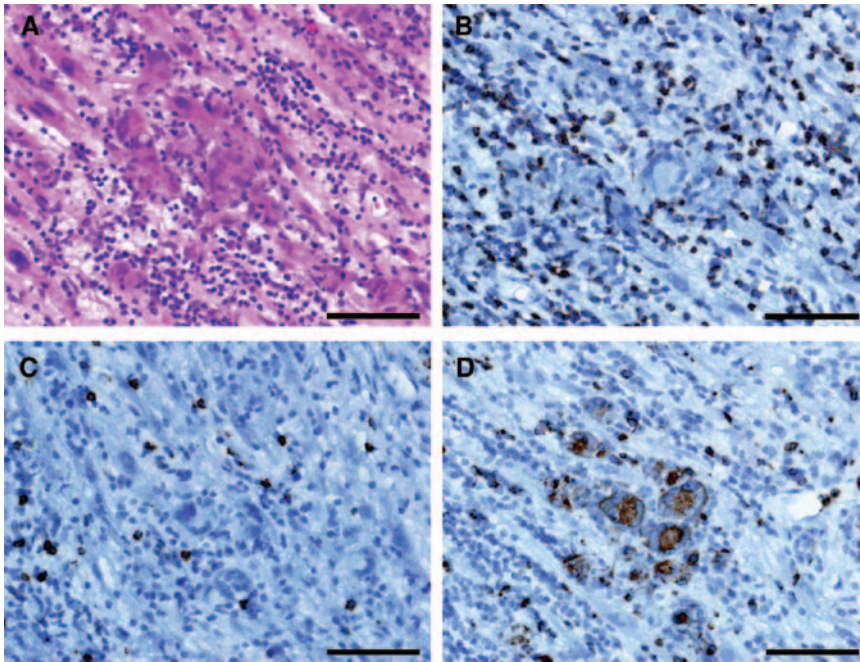


Figure 4. Immunohistochemical features of atrial giant cell myocarditis (GCM). Representative photomicrographs of atrial myocardium from patient with atrial GCM. The atrial myocardium is infiltrated by giant cells and lymphocytic infiltrates with associated cardiomyocyte necrosis (A, hematoxylin and eosin). Immunohistochemical staining for CD3 (B), CD20 (C), and CD68 (D) shows a CD3-positive T cell-predominant infiltrate with scattered CD20-positive B cells and numerous CD68-positive macrophages/histiocytes, including CD68-positive giant cells (brown pigment indicates positive reaction, hematoxylin counterstain). Bars, 100 μ m.

consequences of aGCM are primarily related to atrial dysfunction, including atrial fibrillation/flutter, thrombosis, and cerebrovascular embolic events. These consequences may be mitigated by anticoagulation therapy, although an appropriate therapeutic range in this disorder has not been established.

Occasional cases are more severe, with acute biatrial dysfunction and secondary heart failure, and may require more aggressive intervention. Atrial wall thickening may be an echocardiographic clue in such patients, especially when isolated atrial edema is also observed on T2-weighted imaging. Although Case 3 displayed dramatic clinical improvement after immunomodulation with steroids and cyclosporine, to our knowledge this is the first patient with atrial GCM to be treated in this manner, and the utility of immunosuppression for severe aGCM remains unknown. Additional studies will therefore be required before conclusions can be made regarding the clinical safety and efficacy of this approach.

The incidence of aGCM is unknown. Unfortunately, many institutions are not routinely submitting resected atrial tissues to pathology for evaluation, and other pathology departments are signing out these specimens after gross examination only.

At major referral centers, estimation of incidence based on pathological consultation material is subject to selection bias. Despite these limitations, aGCM may be more common than is generally recognized.

In their 1965 series, Husband and Lannigan reported 3 cases of aGCM among 465 resected left atrial appendages at their institution, corresponding to a frequency of 0.6%.¹⁵ More recently, a single case of aGCM was reported at Stanford University,¹⁷ an institution at which 263 resected atrial specimens were evaluated over an 8-year period (2004–2011; 211 adult, 52 pediatric), for an overall aGCM frequency of 0.4% and a frequency among adult cases of 0.5% (Gerald J. Berry, MD, personal communication).

In our study, 4 cases of aGCM were referred to us from 3 institutions where microscopic evaluation of all surgically resected atrial appendages is performed per institutional policy. At these institutions, a total of 315 atrial appendages were evaluated over time periods ranging from 2 to 12.5 years, corresponding to an overall frequency of 1.3% and individual institutional frequencies ranging from 0.7% to 4.0% (Onsi W. Kamel, MD, personal communication). Although these frequencies are variable, in some cases they appear to be greater

Table 3. Histopathologic Features of 6 Cases of Atrial GCM

Case #	Location	GCs	PF'd grans	WF'd grans	Myocyte Necrosis	Myocyte Hypertrophy	IF	Lymphs	LM-Like Foci	Eos	PMNs	Vasculitis
1	RA, RAA	1+	0	0	1+	2+	2+	1+	1+	0	0	0
2	LA	3+	3+	0	3+	3+	3+	3+	3+	0	0	0
3	LA, RA, RAA	3+	2+	0	3+	1+	3+	3+	3+	1+	0	1+
4	LAA	3+	3+	0	3+	2+	0	2+	3+	2+	0	0
5	LAA	1+	0	0	3+	3+	2+	3+	3+	2+	1+	0
6	RAA	3+	2+	0	3+	2+	1+	2+	2+	2+	0	0

Eos indicates scattered eosinophils; GCs, giant cells; IF, interstitial fibrosis; GCM, giant cell myocarditis; LA, left atrium; LAA, left atrial appendage; LM, lymphocytic myocarditis; Lymphs, interstitial lymphocytic infiltrates; PF'd-grans, poorly formed granulomas; PMNs, scattered neutrophils; RA, right atrium; RAA, right atrial appendage; and WF'd grans, well-formed granulomas.

than the figure previously reported, suggesting that aGCM may be more common than previously recognized. Larger studies will be required to define the true incidence of this uncommon disorder, and institutional policies mandating routine histopathologic examination of surgically resected atrial tissues may facilitate its recognition.

Etiology and Pathogenesis

Like vGCM, aGCM appears to be associated with autoimmune disorders. As in previously reported cases,^{14,16,18} we confirmed an association with rheumatic valve disease in some patients, suggesting related pathogenetic (possibly immune) mechanisms. It has long been recognized that granulomatous inflammation may be seen in atrial appendages excised from patients undergoing mitral valve replacement for rheumatic mitral stenosis.²¹ In such cases, the inflammatory process is characterized by discreet Aschoff nodules containing Anitschkow cells and occasional Aschoff giant cells, in a multifocal and predominantly endocardial or perivascular distribution, without significant cardiomyocyte necrosis, consistent with a chronic smoldering rheumatic inflammatory process. This pattern is distinctly different from the infiltrates seen in our cases of aGCM, which are much more dramatic and diffuse, with abundant giant cells and extensive cardiomyocyte necrosis. In addition, not all cases of aGCM are associated with rheumatic valve disease, suggesting that aGCM is not simply a variant of classical rheumatic heart disease but is, in fact, a distinct entity.

The pathogenesis of aGCM is currently unknown, although the distinctive, apparent localization of the inflammatory process to the atria suggests that atrium-specific auto-antigens may be involved. It is well-recognized that differential gene expression occurs in atrial and ventricular cardiomyocytes. This contributes to the distinct functional differences between these 2 anatomic chambers, including atrium-specific expression of transcription factors (eg, hairy-related transcription factor 1), structural proteins (eg, atrial myosin light chain 2), ion channels and ion channel regulators (eg, connexin 40, voltage-activated K⁺ channel Kv1.5, inward rectifying K⁺ channel Kir3.1, sarcolipin), and secreted hormones (eg, atrial natriuretic peptide).^{22,23}

That an autoimmune process could show preference for 1 type of cardiomyocyte over another is not surprising, as tissue- and antigen-specific autoimmune reactions are the rule in connective tissue and autoimmune disorders. Additional studies will be necessary to determine which antigens, if any, are mechanistically significant in the pathogenesis of aGCM.

Histopathologic Differential Diagnosis

The cases reported herein each demonstrate a marked atrial myocardial infiltrate of T lymphocytes with abundant giant cells and associated cardiomyocyte necrosis. This pattern is similar to that which is seen in vGCM, although some differences were also seen. Poorly formed granulomas were identified in 4 of 6 cases and vasculitis was present in a single case, both of which are not part of the histological spectrum of vGCM. As with vGCM, the differential diagnosis of aGCM includes both infectious and noninfectious entities, which should be excluded before rendering this diagnosis.

Infectious myocarditis may present with granulomatous inflammation and giant cells, particularly in the setting of fungal or mycobacterial infection. Although rare, cases of tuberculous myocarditis²⁴ and fungal myocarditis²⁵ have been reported and often occur in immunocompromised patients. In all of our cases, acid fast and silver stains failed to reveal microorganisms. Although this does not completely exclude the possibility of infection, neither caseation nor heavy neutrophilic infiltrates were seen, making an infectious etiology unlikely.

Cardiac sarcoidosis shares some features with GCM, including the presence of giant cells, although distinction between the 2 can usually be readily made. Black race, syncope, and atrioventricular block are more commonly seen in sarcoidosis than in GCM, and heart failure is more commonly seen in GCM than in sarcoidosis.²⁶ Histologically, granulomas within the myocardium tend to be better formed in sarcoidosis than in GCM. Cardiomyocyte necrosis is generally not a prominent feature of sarcoidosis, unlike in GCM, and eosinophils are not usually prominent.²⁶ All of our patients were white, and their histological features were more similar to GCM than sarcoidosis, thus supporting a diagnosis of aGCM. Although granulomas were present in 4 cases, these were small and poorly formed with extensive associated cardiomyocyte necrosis in each case, making a diagnosis of cardiac sarcoidosis unlikely.

Granulomatosis with polyangiitis (GPA, formerly known as Wegener granulomatosis) may occasionally involve the heart and show variable histological findings, including necrotizing vasculitis, granulomas, or giant cells.^{27,28} Granulomas were present in 3 of the present cases but were non-necrotizing, unlike those of GPA, and geographic necrosis was not identified. In a single case, vasculitis was present but was focal and non-necrotizing, unlike the vasculitic lesions of GPA. In all cases, the findings were consistent with GCM and not typical for GPA, but difficult cases may require serum studies for anti-nuclear cytoplasmic antibodies to distinguish these entities.

Conclusion

We believe atrial GCM represents a distinct clinicopathologic entity with a more favorable prognosis than classic idiopathic ventricular GCM. This disorder should be included in the differential diagnosis of atrial dilatation, particularly when associated with atrial wall thickening and edema. Cardiac imaging findings are distinctive and should prompt consideration of this entity. Most cases of atrial GCM behave in a relatively indolent fashion, although some cases may be symptomatic. The therapeutic utility of immunosuppressive agents for this condition remains unknown.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Idiopathic giant cell myocarditis (GCM) is a rare and particularly aggressive form of myocarditis, characterized by myocardial destruction attributable to dense lymphohistiocytic inflammation, including abundant giant cells. GCM typically causes fulminant heart failure, arrhythmias, or heart block, and left untreated, is almost universally and rapidly fatal. Current treatment approaches have modestly improved survival, including aggressive immunosuppression and ventricular assist device insertion, but prognosis remains poor and many patients eventually require heart transplantation. We describe a novel variant of GCM, primarily involving the atria, that displays distinctive clinical features and follows a more benign course than ventricular GCM. Clinically, most patients are diagnosed incidentally during routine pathologic evaluation of atrial tissues removed during cardiac surgery for other indications (eg, valve replacement or coronary bypass grafting). Nearly all are in atrial fibrillation. Imaging findings include severe atrial dilatation, mitral/tricuspid regurgitation, atrial mural thrombus, atrial wall thickening, and atrial hypokinesis, with preserved ventricular function. Pathologically, atrial tissues show findings remarkably similar to classical ventricular GCM. Most patients do very well with supportive care, and return to baseline exercise tolerance within weeks to a few months. Atrial GCM represents a distinct clinicopathologic entity with a more favorable prognosis than classic ventricular GCM. This disorder should be included in the differential diagnosis of atrial dilatation, particularly when associated with atrial wall thickening. Although the radiologic and pathologic findings are striking, recognition of this disorder by clinicians, radiologists, and pathologists is important to avoid overtreatment. The utility of immunomodulatory therapy for this condition remains unknown.

Atrial Giant Cell Myocarditis: A Distinctive Clinicopathologic Entity

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