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Case Report

A Rare Case of Giant Cell Myocarditis

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ABSTRACT

Giant cell myocarditis is a rare condition first described in 1905. It has a reported incidence range from 0.007% to 0.051%. It affects female and male individuals, equally, and usually occurs in young and middle-aged persons. The underlying aetiology of giant cell myocarditis is unknown but it is thought to be mediated by T-lymphocytes. Diagnosis is made *via* histological examination of myocardial tissue and is characterized by a mixed inflammatory cell infiltrate with multinucleated giant cells and cardiomyocyte necrosis, predominantly affecting the ventricles. The following report describes a rare case of giant cell myocarditis in a 71-year-old man with a history of hypertension and heart failure, who died while waiting to be seen in the emergency department. Autopsy findings revealed an enlarged, dilated heart with histologic features in keeping with giant cell myocarditis, along with features of heart failure. Diagnosis of giant cell myocarditis is less common in the elderly age group, possibly due to a less severe disease process in this age group and it may be misdiagnosed because older individuals may have other cardiovascular diseases (CVDs).

Keywords
Myocarditis; Giant cell myocarditis; Autopsy; Elderly, Cardiovascular.

INTRODUCTION

Giant cell myocarditis (GCM) is an uncommon entity. It is a rare condition, and is usually described as a disease that is rapidly progressive and frequently fatal. Idiopathic GCM was first described by Salty kow in1905, at autopsy and, most, if not all cases of GCM between 1905 and up to the mid-1980's, were diagnosed at autopsy.[1,2] It is a histologic diagnosis and it is characterized by a mixed inflammatory cell infiltrate within the myocardium, predominantly composed of lymphocytes, along with plasma cells, eosinophils and fewer neutrophils, Multinucleated giant cells are additionally present, as is cardiomyocyte necrosis.[2-4] Sometimes, there may be poorly formed granulomas. The histologic changes of GCM mainly affects the ventricles.

Historically, GCM and cardiac sarcoidosis (first described by Bernstein in 1929) were not properly differentiated, as both presented similarly, and could result in a myocarditis characterized by giant cells and granulomas.[2,5] Nevertheless, they have since been established as two distinct clinicopathologic entities with significant differences in presentation, histologic features, and prognosis.[2] The underlying aetiology of giant cell myocarditis is unknown but it is thought to be mediated by T-lymphocytes.[2,3]

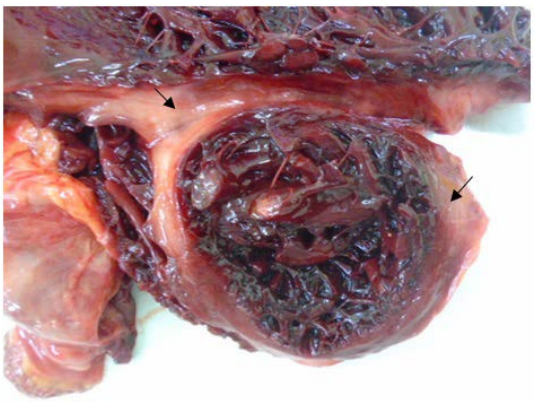
The incidence of GCM has been reported to range from 0.007 to 0.051% (predominantly autopsy data) and mainly occurs in young to middle aged individuals.[2-4,6] However, it is likely that the true incidence of GCM has been underestimated, given that autopsy rates have decreased worldwide and are not routinely performed on most individuals, and, hence, patients dying of GCM may not undergo autopsy.[7] Here we describe an undiagnosed case of GCM in a 71-year-old man.

CASE REPORT

This 71-year-old man had a clinical history of hypertension with heart failure (duration unknown) and was maintained on diuretics. He presented to a rural hospital with a two-day history of difficulty

breathing. He had a long waiting time in the emergency room (>7 hours), and while waiting to be seen, he collapsed and struck his head on the wall. He was assessed as being in cardiac arrest. Cardiopulmonary resuscitation was commenced but was unsuccessful and he was pronounced dead after 1-hour of resuscitative efforts. At autopsy, the body was that of an elderly man, with an oval, red, 12×7 cm haematoma on the centre of the forehead. There were no underlying skull fractures. There was no evidence of meningeal or intraparenchymal cerebral haemorrhage. He had an enlarged heart that was dilated, and weighed 500 g, with left ventricular wall thickness of 1 cm. The cut-surface of the left ventricle was somewhat salmon pink and firm (Figure 1). The heart had the usual anatomic arrangement of chambers and great vessels and the coronary arteries were patent. He had bilateral pleural effusions and multiorgan congestion, consistent with heart failure.

Figure 1. *Cross Section of the Left Ventricle of the Heart Depicting Concentric Fibrosis of the Wall. The Fibrous Tissue is Grey-White in Colour (black arrows). The Left Ventricular Cavity is also Dilated*



Histologic examination of the decedent's heart revealed chronic, mixed, inflammatory cell infiltrate involving the outer half of the myocardium, which was associated with extensive, circumferential fibrosis (Figure 2). The inflammatory cell infiltrate was composed predominately of lymphocytes and multinucleated giant cells, in the absence of granulomas (Figures 3a and 3b). There was reparative cardiomyocyte hypertrophy. Special stains including gomori methenamine silver and Congo red stains, were negative (Figures 4a, 4b and 5). The overall histologic features were in keeping with giant cell myocarditis.

Figure 2. *Chronic Myocarditis with Involvement of the Outer Half of the Myocardium, Associated with Extensive Fibrosis (black stars). There are Intact Nyocardiocytes in between the Fibrous Tissue (40x)*

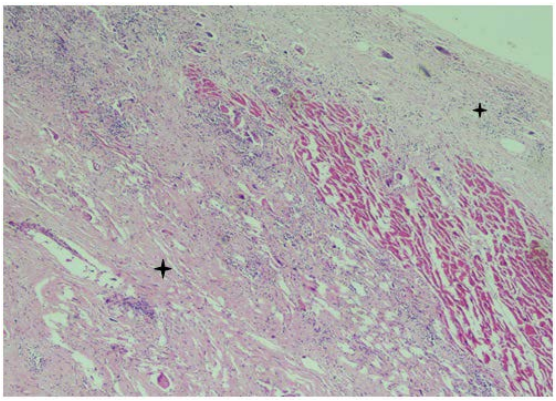


Figure 3a. *Chronic Inflammatory Cell Infiltrate Composed of Lymphocytes (orangestar) and Multinucleated Giant Cells (grey arrows) (100x)*

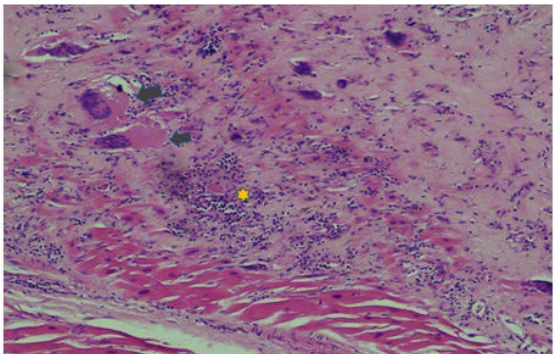


Figure 3b. *Chronic Inflammatory Cell Infiltrate Composed of Lymphocytes (orange star) and Multinucleated Giant Cells (grey arrow) (200x)*

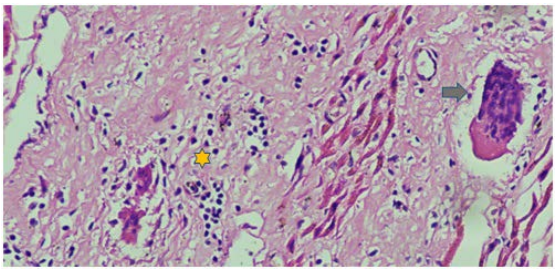
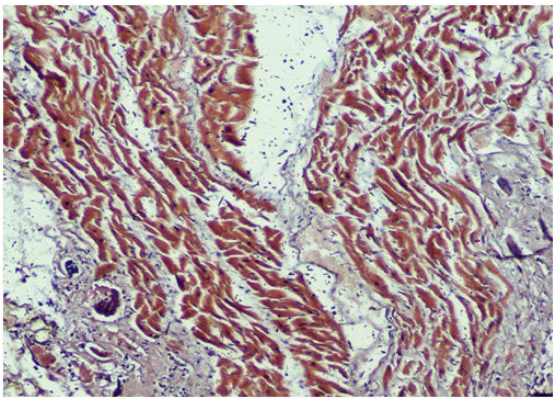


Figure 4a. *Negative Congo Red Stain of Myocardium (100x)*



Histology of the lungs revealed fibrosis of the visceral pleura, an organizing micro-thrombus, moderate vascular congestion and pulmonary oedema. There was chronic passive congestion of the liver. There was no evidence of end-organ-kidney changes of hypertension.

Figure 4b. *Negative Congo red Stain of Myocardium (100x)*

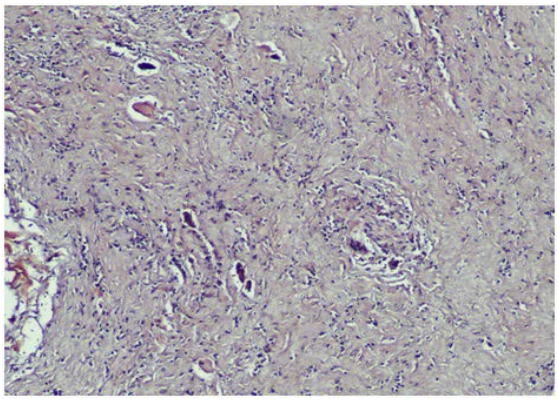
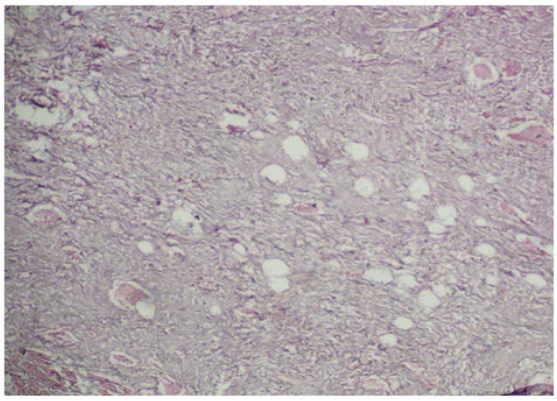


Figure 5. *Negative Silver Stain of Myocardium (100x)*



DISCUSSION

Giant cell myocarditis is a rare condition, the underlying aetiology is unknown, but, it is thought to be mediated by T-lymphocytes.[2,3] It is reported to be associated with other autoimmune diseases (e.g. Hashimoto's thyroiditis, myasthenia gravis, orbital myositis) and tumours of immune cells (e.g. lymphoma), in approximately 20% of cases, suggesting that autoimmunity may play a role in its development.[2,3] There is no male to female discordance as it affects male and female individuals in equal numbers. It can affect individuals of any age, although, the majority of cases occur in young or middle-aged adults (median age 42-years).[6] However, it could be proposed that the relative infrequency of reported cases in the elderly could be partially attributed to a less fulminant course of the disease in this age group, in addition to a decreased level of suspicion in these persons who may often have other cardiovascular diseases.[8] The latter could be the proposed reason as to why such a diagnosis might not have been made, clinically, in the decedent in the current case report.

GCM usually affects the ventricles of the heart and diagnosis is made *via* light microscopy (histology). It ischaracterized by a mixed myocardial inflammatory cell infiltrate, predominantly within the ventricles and composed of lymphocytes along with plasma cells, eosinophils, fewer neutrophils and multinucleated giant cells. Cardiomyocyte necrosis is also present and poorly formed granulomas, may be seen.[2]

Diagnosis is made *via* endomyocardial biopsies (usually), or occasionally by wedge biopsies; but, even in experienced centres, more than 4 in 10 cases may be missed after endomyocardial biopsies have been performed and diagnosis is made only at autopsy or after examination of a cardiac explant.[2,8,9] These false negative findings may be due to the patchy nature of the inflammatory disease, previous treatment of other entities, thereby masking the findings of GCM, or inadequate sampling.[2] Also, sampling may not reveal the multinucleated giant cells, and a misdiagnosis of lymphocytic myocarditis might be made instead. Furthermore, there are other myocardial pathologic entities that are associated with giant cells, and these entities will need to be ruled out, prior to establishing a diagnosis of GCM. Such differential diagnoses include infectious diseases, systemic granulomatous processes, and foreign body giant cell reaction granulomatous diseases.[2] They can be ruled out by using histologic ancillary stains such as silver or Ziehl–Neelsen special stains, if granulomatous inflammation is seen. Masson's trichrome or Movat pentachrome special stains can be used to highlight interstitial fibrosis, myocyte disarray, and necrosis. Iron stain in male and postmenopausal female patients can be performed to rule out a potentially treatable iron storage disease. Congo red stain may be performed to rule out cardiac amyloidosis, which often occurs in the elderly. Polymerase chain reaction (PCR), if available, could be attempted to detect viral genomes, in chronic lymphocytic myocarditis.[2]

As previously mentioned, a misdiagnosis of chronic lymphocytic myocarditis may be made instead of GCM, histologically. However, the clinical course of chronic lymphocytic myocarditis is more variable with individuals presenting with asymptomatic electrocardiographic or echocardiographic abnormalities or with acute myocardial infarction-like syndrome, overt congestive heart failure, cardiogenic shock, and death, while the clinical course of GCM on the other hand is usually characterized by rapidly progressive congestive heart failure, frequently associated with ventricular arrhythmia.[2,10] Most patients with GCM (≥75%) present with rapid-onset congestive heart failure, but other presenting symptoms and signs include refractory ventricular tachycardia, complete heart block and acute myocardial infarction.[2,3,8,9,11,12] Sudden death is a less common presentation.

According to most medical literature, the median survival time is ~3 months, without immunosuppressive therapy.[13] Therefore, once the diagnosis has been made, individuals can be treated with immunosuppressive therapy inclusive of cyclosporin, to help improve long-term survival, but the effects are short-lived and most persons die as a result of cardiac failure or arrhythmia. Cardiac transplantation is proposed, therefore, as the treatment of choice. However, even then, there is the possibility of fatal disease recurrence following cardiac transplantation (~25% of cases), thus the efficacy of cardiac transplantation has been questioned.[2-4,11]

Newer medical literature has shown that GCM is not always rapidly progressive and fatal, even in the absence of immune

suppression or transplantation. Instead, individuals with GCM may present clinically with an atrial variant and this atrial form has a less fulminant course. Also, individuals with GCM maybe disguised/misdiagnosed for years as having a monosymptomatic heart block or dilated cardiomyopathy.[2,14,15] Transplant-free survival, well beyond 15-years of diagnosis, has also been reported.[6] Ekström et al showed that there were stand-alone factors that could determine persons survivability, even without immunosuppressive therapy.[13] They showed that the severity of myocardial injury, and to a lesser degree, cardiac dysfunction at presentation, constituted the key predictors of transplant-free cardiac survival in GCM.[13]

CONCLUSION

Giant cell myocarditis is an uncommon clinical disease, which has been classically described as a rapidly progressive disease with a high mortality. Its underlying aetiology is unknown, but it is believed to be mediated by T-lymphocytes. Although it is not a histologically challenging diagnosis, the clinical diagnosis is not commonly made or entertained. Unfortunately, most cases are diagnosed at autopsy or after cardiac transplantation. Therefore, it is important that clinicians always keep giant cell myocarditis as a potential differential diagnosis when patients present with rapidly progressive congestive heart failure, especially when associated with ventricular arrhythmia. Also, where possible, endomyocardial biopsies of the atria should be included, along with the usual biopsies of the ventricles, as there can be an atrial variant of this disorder, which has a less fulminant course.

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