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Giant Cell Myocarditis in Children

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Abstract

Giant cell myocarditis is a rare cause of heart failure and arrhythmias in children. In the multicenter GCM registry, 4 of 63 cases (6%) occurred in subjects less than age 19. In this manuscript, these 4 cases are summarized and the findings related to other published reports. Unlike pediatric lymphocytic myocarditis, that generally has a good prognosis despite a fulminant clinical course, GCM usually results in death or heart transplantation. In children as in adults, GCM can often be distinguished clinically by a failure to respond to usual care and the frequent occurrence of ventricular arrhythmias or heart block in the setting of acute cardiomyopathy. GCM is also associated with other immune-mediated disorders in about 20% of patients. In children associated immune-mediated disorders have only been observed in females. Prompt endomyocardial biopsy in the setting of suspected GCM can affect choice of mechanical circulatory support (MCS), lead to early listing for cardiac transplantation, and consideration of cyclosporine-based immunosuppression.

Keywords

Myocarditis; Giant Cell Myocarditis; Heart Failure; Endomyocardial Biopsy

Introduction

The first case of giant cell myocarditis (GCM) in a child was published in 1955.[1] All 19 children with GCM reported since the first case have died or required heart transplantation after a brief illness.[2] Although cases of pediatric GCM are infrequent, an analysis of the published data permits preliminary conclusions regarding the natural history, benefits of mechanical circulatory support (MCS), immunosuppression, and transplantation in children with GCM.

Pediatric cases of GCM in the Multicenter GCM Registry

Four of the 63 cases of GCM reported in the multicenter GCM registry occurred in children younger than age 19. These 4 cases were included collectively in the 1997 registry report,[3] but the individual data have not been previously published. We will briefly review the salient features of each of these cases in order to frame the following discussion of pediatric GCM.

Case 1

An 18 year old boy presented with dyspnea 3 weeks after an upper respiratory tract infection. He had no relevant past medical history including no immune-mediated disorders. He also

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reported palpitations and was found to have ventricular tachycardia and supraventricular tachycardia. The left ventricular ejection fraction was estimated at 35% by echocardiogram. Endomyocardial biopsy revealed typical giant cell myocarditis. He was treated with a combination of cyclosporine, azathioprine, and steroids with modest improvement in cardiac function and arrhythmias. Unfortunately, he developed recurrence of arrhythmias and gradual deterioration of cardiac function over the subsequent 36 months. He underwent heart transplantation and died 4 weeks postoperatively of multiorgan system failure.

Case 2

A 17 year old boy with no history of immune-mediated disorders presented with 4 weeks of fatigue and progressive dyspnea. He was found to be in heart failure with no reported arrhythmias. The left and right ventricular ejection fractions measured by radionucleotide angiography were 18% and 14%. Right ventricular endomyocardial biopsy revealed GCM. He required MCS with a Jarvik artificial heart and underwent successful transplantation 1 week later. After 3 years, there was no recurrence of GCM in the donor heart.

Case 3

A 16 year old girl presented with several weeks of progressive dyspnea and was found to be in left ventricular heart failure. Her history was remarkable for possible inflammatory bowel disease, psoriasis, and recent insulin dependent diabetes. She was diagnosed with GCM by endomyocardial biopsy and treated with intravenous immunoglobulin and steroids. Despite supportive care, she developed ventricular arrhythmias and expired approximately 4 weeks after the development of heart failure symptoms.

Case 4

A 17 year old boy presented with fatigue and dyspnea for approximately 10 days. He had no reported arrhythmias, but required a left ventricular Novacor assist device for progressive cardiac failure. The diagnosis of GCM was made from the apical core. He was not treated with immunosuppressive medication, but developed progressive right ventricular failure. He underwent heart transplantation on post-implant day 60 and expired 1 day following transplantation.

These cases suggest that like the presentation of GCM in adults, the presentation in children is usually acute heart failure. In a review by Das, et al, 10 of the 14 children with available data presented with heart failure, 5 with ventricular tachycardia, and 1 with complete heart block. These proportions are similar to those in the 63 subjects reported in the multicenter GCM registry of which 75% presented with heart failure, 15% with ventricular tachycardia, 5% with complete heart block, and 6% with an acute coronary-like syndrome.[3]

In contrast to acute GCM, lymphocytic myocarditis in children generally has a good short term prognosis when diagnosed by endomyocardial biopsy. In an Australian study of dilated cardiomyopathy in children less than age 10, Daubeney, and colleagues reported a 100% 10 year transplant-free survival in 13 children diagnosed by biopsy.[4] However, 12 of the 25 children with lymphocytic myocarditis in this study were diagnosed by autopsy. It is not clear whether there was a difference in clinical presentation or treatment effect between the 2 groups of children that could explain the dramatic outcome difference. In the North American pediatric cardiomyopathy registry, Towbin, and colleagues reported that the prognosis of lymphocytic myocarditis was also better than noninflammatory dilated cardiomyopathy in children diagnosed by biopsy.[5]

However in the 222 children with myocarditis, there was a late risk of death or transplantation between 5 and 10 years after diagnosis which was not observed in the Australian series.

GCM in children is associated with immune-mediated disorders in a substantial minority of cases. One of the 4 children in the GCM registry had possible inflammatory bowel disease, psoriasis, and insulin dependent diabetes. In the Das, et al. review, common variable immune deficiency, ulcerative colitis, and myositis were each reported in 1 case. Thus 22% (4/18) pediatric GCM cases have been associated with immunologic disorders in other organs, a rate similar to the rate in the adult population.[3] Interestingly, the 3 cases from the Das review and the case from the present series were female. Furthermore, all cases of thymoma-associated GCM have been reported in women.[6] Overall, the rate of GCM is equal in males and females. Therefore, as compared to the disease in males, GCM in females may be more commonly associated with autoimmune disease in other organs.

The clinical course of GCM is usually a rapid deterioration in cardiac function over several days to weeks. The mean time from symptom onset to diagnosis for all subjects in the GCM registry was 4 weeks, and the mean time to death or transplantation was 5.5 months.[3] The clinical course is at least as rapid in the pediatric population, with a mean time from symptom onset to death, transplant, or MCS of 15 days in the 3 subjects not treated with cyclosporine based immunosuppression. The one boy treated with cyclosporine, azathioprine, and steroids survived 3 years until transplantation.

Treatment with immunosuppression that includes cyclosporine has been associated with prolonged transplant-free survival in subjects with acute GCM. In the multicenter GCM registry, Patients treated without immunosuppressive therapy had a median transplant-free survival of 3.0 months, compared to a 12.3-month ($p=0.003$) median transplant-free survival for patients treated with cyclosporine-based immunosuppression.[3] In a prospective study of 11 patients with acute GCM treated with cyclosporine and steroids (usually given with 10 days of muromonab-CD3), 10 survived at least 1 year and only 2 underwent heart transplantation.[7] The one death that occurred after the 1 year primary endpoint was due to fulminant, recurrent GCM in a subject who had stopped all immunosuppression. The only available data regarding cyclosporine-based immunosuppression in the pediatric population is our case number 4, who also had prolonged transplant-free survival.

The role of MCS and heart transplantation in children with GCM has recently been reviewed by Das, et al.[2] They report that extracorporeal membrane oxygenation or a ventricular assist device is usually needed as a bridge to transplantation. However, a limitation of their data is that few children were treated with immunosuppression prior to transplantation. In our subject who received a Novacor LVAD, there was progressive deterioration in right ventricular function. This suggests that there may be a role for biventricular device support early if the diagnosis of GCM is known at the time of MCS implantation. There was 1 recurrence out of 6 transplants, which is similar to the 20–25% rate observed in the adult population.[8,9] The optimal immunosuppressive strategy following transplant is not known, but careful monitoring for possible recurrence is warranted. In contrast to the aggressive course of GCM recurrence in the pediatric case, the course of post-transplant GCM is relatively mild in adult case series. Indeed, most histological recurrences in adults occurred during routine surveillance biopsies.[3]

GCM is not the only disorder associated with giant cells in the heart. The pathologic criteria for GCM are a diffuse or multifocal inflammatory infiltrate consisting of lymphocytes with multinucleated giant cells. The giant cells are usually at the edges of the inflammatory lesions and are frequently associated with intact and degranulated eosinophils. Myocyte damage is always present in association with the inflammatory lesion. Varying degrees of fibrosis may be present. Although poorly formed granulomas may be seen in giant cell myocarditis, fibrosis is rarely widespread and well-organized, follicular granulomas containing central giant cells strongly favor a diagnosis of cardiac sarcoidosis. Other disorders which should be excluded

by clinical and pathologic appearance include rheumatic fever (with Ashoff nodules), foreign body reaction, and Wegener's granulomatosis.

In summary, the clinical reports of GCM in children suggest that the disease has some similarities and a potentially a few important differences compared to GCM in adults. Specifically, adult and pediatric GCM are similar with respect to the presenting symptoms, clinical course and prognosis before transplantation. In contrast to the disease in adults, GCM has only been observed in association with immune disease in other organs in females and the clinical course of GCM recurrence following transplant may be more aggressive than in the adult population, in whom most histological recurrences are asymptomatic.[9]

Insights from the larger adult population may also impact the treatment of children. Endomyocardial biopsy should be strongly considered for suspected GCM in pediatric patients who have acute heart failure of unknown cause that fails to respond to usual care or is associated with heart block and/or ventricular tachycardia. It is unknown whether the treatment of GCM with cyclosporine-based immunosuppression may delay time to transplantation or prolong survival in children. However, an early diagnosis of GCM may allow for prompt heart transplantation evaluation and possibly affect the choice of MCS. Future investigation should include reports regarding the efficacy and safety of immunosuppression for pediatric GCM.

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