CASE REPORT

Giant cell myocarditis presenting with acute heart failure

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SUMMARY

Idiopathic giant cell myocarditis (GCM) is a rare and rapidly progressing form of myocarditis predominantly affecting younger people. We report a case of a 23-year-old athletic patient who presented with features of acute heart failure due to GCM and discuss his management that included a left ventricular assist device as a bridge to transplant. He died immediately following the transplant.

We also review the literature on this rare disease, highlighting the advances in the management of the disease including immunosuppressive therapy, ventricular assist devices and heart transplantation.

BACKGROUND

Idiopathic giant cell myocarditis (GCM) is a rare and rapidly progressing form of myocarditis predominantly affecting younger people. The GCM study group has reported 63 cases in people between 16 and 69 years old at the time of the diagnosis.¹ The youngest reported case of GCM was in a 6-week infant and the oldest in a patient aged 88 years.^{2,3} We report a case and review the literature.

CASE PRESENTATION

A 23-year-old white Caucasian male with no previous background of heart disease presented with a 6-week history of increasing shortness of breath and a 1-day history of dull chest pain and pedal oedema. He had no family history of cardiac problems, was a non-smoker with minimal alcohol consumption, no use of illicit drugs and no foreign travel. He played football and semiprofessional tennis regularly. In retrospect, he reported having been unwell for around 6 months, although he only presented when he became acutely unwell.

INVESTIGATIONS

His heart rate was 90 per minute, in sinus rhythm, and his blood pressure was 103/70 mm Hg. His jugular venous pressure was 10 cm H₂O, and he had bilateral pitting oedema to mid-shin. He had no additional heart sounds. His ECG was normal, but his echocardiogram showed severe global left ventricular systolic dysfunction with possible LV apical thrombus. His right ventricle was dilated and severely impaired. His haemoglobin was 108 g/L, albumin was 24 g/L and troponin T was 370 ng/L. A CT pulmonary angiogram showed a small subsegmental pulmonary embolus.

Cardiac MRI showed severe impairment of both left and right ventricular systolic function with a pattern of gadolinium enhancement suggestive of myocarditis (figure 1A) and confirmed an LV thrombus (figure 1B). Coronary angiography was normal. His ferritin, thyroid stimulating hormone (TSH), B12 and folate were normal, while his transferrin saturation was low with a low iron of 7 µmol/L, for which he had an iron infusion. Investigations including urine/serum electrophoresis, anti-nuclear antibodies and viral screen for myocarditis were negative. Initial NT-pro-BNP was 17 371 ng/L. He responded well to furosemide, ramipril, digoxin, carvedilol, eplerenone and warfarin.

Two weeks following discharge, he re-presented with abdominal bloating, exhaustion and lethargy on minimal exertion. He had ascites that responded to intravenous furosemide. His ramipril was decreased for hypotension, and he was started on ivabradine as his heart rate was 75 bpm. Right heart catheterisation showed that his cardiac output was 1.2 L/min (index of 0.9 L/min/m). His right-sided pressures were all identical suggesting the right heart was contributing little to the circulation. Pulmonary vascular resistance was 1 Wood unit. N-terminal prohormone of brain natriuretic peptide at the time was 4847 ng/L.

TREATMENT

He was referred for consideration of cardiac transplantation and had a HeartWare left ventricular assist device (LVAD) implanted with a temporary right ventricular assist device (RVAD) to assist postoperative management of right ventricular failure. Histology of the apical core removed at the time of the LVAD implantation revealed patchy severe inflammatory infiltrates composed of mature lymphocytes, histiocytes, plasma cells and numerous multinucleated giant cells.

A cardiac resynchronisation defibrillator was implanted. He made a successful recovery but continued to have atrial fibrillation, which terminated with intravenous amiodarone. After recovery of his RV function, the temporary RVAD was removed.

OUTCOME AND FOLLOW-UP

While still in hospital at 8 weeks after LVAD implantation, he received a heart transplant; however, he died 4 days postoperatively from a stroke (25 weeks following initial presentation). The gross examination of the explanted heart showed multiple

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Figure 1 (A) Cardiac magnetic resonance imaging (CMR) demonstrating delayed gadolinium hyperenhancement of right ventricular free wall, in the RV side of the interventricular septum, subepicardial layer of the apical lateral free wall and left ventricular (LV) apex consistent with myocardial necrosis (arrows). T1-weighted two-chamber image with fat saturation taken 10 min postgadolinium (T_{in}version time: 250 ms, field of view (FOV) 350 cm, echo time (TE) 2 ms, TR 4 ms). (B) CMR demonstrating a small LV thrombus (arrow). T1-weighted four-chamber two-dimensional image taken immediately postgadolinium looking for LV thrombus (T_{in}version time: 600 ms, FOV: 350 cm, TE: 2 ms, repetition time (TR): 4 ms).

well-delimited inflammatory lesions in different areas of the myocardium (figure 2A). Microscopic examination of these lesions (figure 2B–D) was identical to the LVAD biopsy.

DISCUSSION

Background

The aetiology of GCM is unknown. The majority of cases (up to 81%) happen in otherwise healthy young individuals.^{1 4 5} There

Figure 2 (A) Macroscopic appearances of the left ventricular wall with yellow/whitish inflammatory lesions in the subepicardium (thick arrow) and midmyocardium (thin arrow) along with a fibrotic lesion in the subendocardium (curved arrow). (B) Subepicardial area with a focus of severe dense diffuse inflammation advancing from right side, sparing an area of myocardium at the left edge of the field (H&E $\times 40$). (C) Inflammatory infiltrate through damaged myocardium showing numerous multinucleated giant cells without any evidence of granulomata organisation (H&E $\times 200$). (D) Detail of the inflammatory infiltrate composed of mononuclear cells admixed with multinucleated giant cells causing myocytic damage (H&E $\times 200$).

Box 1 Autoimmune and other diseases associated with giant cell myocarditis

- ▶ Crohn's disease¹
- ▶ Ulcerative colitis¹
- ▶ Thyroid disease¹
- ▶ Cryofibrinogenaemia¹
- ▶ Common variable immunodeficiency¹⁰
- ▶ Pernicious anaemia¹⁰
- ▶ Lymphoma¹⁰
- ▶ Rheumatoid arthritis¹⁰
- ▶ Thymoma¹
- ▶ Optic neuritis¹

may be an association with autoimmune disorders in perhaps 20% on the basis of case reports (box 1), with inflammatory bowel disease in several cases (up to 8% in one study). Lewis rats develop GCM when immunised with cardiac myosin suggesting an autoimmune origin. CD4⁺ T lymphocytes were the main cell type implicated in the initial phase of the disease in the rat model,⁶ whereas in human GCM CD8⁺ T cells predominate.⁷ One study reported that while CD8⁺ cells may outnumber CD4⁺ in the acute stage of the disease in human GCM, the CD4⁺/CD8⁺ ratio varies at different stages of the disease.^{5,7}

A prominent eosinophilia has also been described in acute GCM. Serum and IgG from diseased rats does not cause GCM in healthy rats, again suggesting that T-lymphocytes are implicated. However, when lymphocytes from myosin-immunised animals were activated by concanavalin A and infused into healthy rats, the healthy rats did develop GCM.⁸

Why would a normal individual develop an immune reaction to myosin? Hazebroek *et al* reported the case of a 50-year-old cyclist (performing >6000 km/year for 15 years). He presented with biventricular dilation and had biopsy features of GCM as well as low-load human herpes virus-6 and parvovirus 19 infection.

The authors speculated that the endurance training might have led to overload-induced RV cardiomyopathy, which might have predisposed him to viral infection and localised ischaemia, and that the sudden deterioration might have been due to this chronic myocardial inflammation.⁹ Endurance exercise can cause dilation of the right heart and in prone individuals patchy myocardial scarring might occur. MR scanning in a group of athletes (12.5%) competing in large cumulative endurance events showed scarring and RV remodelling.^{10 11}

Diagnosis and management

Patients with GCM present with features of rapidly progressing congestive heart failure. Less commonly, the presentation may resemble acute myocardial infarction or present as unexplained sudden cardiac death.^{1 12-14} In the multicentre GCM registry up to 75% of patients presented with heart failure, with 14% presenting with ventricular tachycardia (VT), 6% with a syndrome resembling a myocardial infarction and 5% with atrioventricular block.¹

The definitive diagnosis of GCM is made by histological examination of endomyocardial surgical biopsy, explanted heart or at postmortem examination. One recent case series reported the sensitivity of endomyocardial biopsy to be 68% after one biopsy, increasing to 93% after two or three biopsies.¹⁵ Typical histological findings are widespread mixed inflammatory infiltrates including histiocytes, T lymphocytes and multinucleated

giant cells causing myocytic damage. The absence of sarcoid granulomata distinguishes it from cardiac sarcoidosis.^{1 15} There are reports of other disorders causing myocardial granulomas with giant cells, which can be confused with idiopathic GCM. The Aschoff lesions seen in rheumatic myocarditis can progress into focal interstitial granulomas with associated giant cells. The presence of giant cells within granulomatous lesions has also been described in patients with tuberculosis, cryptococcosis and very rarely syphilitic myocarditis. Special stains should be performed if an infectious cause is suspected. Part of the differential should also include Wegener's granulomatosis, foreign body reaction, along with systemic sarcoidosis.¹⁴

If the presenting features are those of rapidly progressing heart failure and/or there is persistent release of troponin T, then early biopsy is indicated. Gadolinium-enhanced cardiac magnetic resonance imaging and 18F-fluorodeoxyglucose-positron emission tomography are useful to localise areas of inflammatory myocardial damage and scarring, identifying target areas for biopsies.¹⁵

The median survival time from onset of symptoms to death was estimated at 5.5 months without transplantation or ventricular assist device (VAD) implantation in the GCM study group. The rate of death or heart transplantation was 89% at 5 years, much higher than the 56% in lymphocytic myocarditis.^{1 16} Treatment with immunosuppressive agents (eg, cyclosporine, azathioprine, corticosteroids or anti T lymphocyte antibodies) may prolong the time to transplantation and survival compared with no immunosuppression.^{1 17} A single-centre study of 32 patients showed transplant-free survival from symptom onset at 1, 2 and 3 years to be 69%, 58% and 52%, respectively. Of the 32 patients, 26 were treated with combined immunosuppression and at a median follow-up of 14.5 months, 22 (85%) were still alive with 17 (65%) free of transplantation.¹⁵ VADs can be vital to bridge a patient to transplantation, especially with rapid deterioration. A particular problem is that the right ventricle is often involved in the disease process, meaning that both ventricles may have to be supported.¹⁷

GCM may recur in the transplanted heart. The largest multi-centre study reported recurrence in 9 of 34 patients transplanted for GCM (26%).^{1 17} Of the nine patients, three had clinical

disease, responding to aggressive immunosuppressive therapy in two. In the remainder, the diagnosis was made on biopsy, and 5 out of 6 were well at an average of 2.1 years from recurrence.¹

Contributors IK participated directly in the care of the patient and drafted the manuscript. JM analysed pathological specimen and participated in the writing of the manuscript. GM participated directly in the care of the patient and participated in the writing of the manuscript. AC participated directly in the care of the patient and supervised IK in the writing of this manuscript. All authors read and approved the final manuscript.

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Learning points

- ▶ Giant cell myocarditis is a rare cause of acute heart failure.
- ▶ GCM follows a very aggressive course.
- ▶ Myocardial biopsy is necessary to establish the diagnosis.
- ▶ Immunosuppressants may improve prognosis.
- ▶ Transplantation is usually necessary, but GCM may recur in the transplanted heart.

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