Adalimumab for the treatment of cardiac sarcoidosis with multiple arrhythmias

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Abstract

A 45-year-old male with cardiac sarcoidosis verified by cardiac biopsy presented with multiple coexisting arrhythmias, including ventricular tachycardia of more than 1000 episodes per 24 h, paroxysmal atrial fibrillation, and third-degree atrioventricular block. He did not respond to corticosteroids dose of 20–60 mg once daily and mycophenolate mofetil dose of 1 g twice daily for 6 months. Cardiac magnetic resonance (CMR) demonstrated inflammation and late gadolinium enhancement on right ventricular wall and interventricular septum. Positron emission tomography-computed tomography (PET-CT) showed multifocal ¹⁸F-fluorodeoxyglucose uptake in the heart. We replaced mycophenolate mofetil with adalimumab, a tumour necrosis factor-α inhibitor. After 3 months, his arrhythmias improved significantly, manifesting as premature ventricular contractions of only 500 beats per 24 h and first-degree atrioventricular block. CMR showed a significant reduction in inflammation and late gadolinium enhancement, and PET-CT showed a complete resolution of fluorodeoxyglucose uptake.

Keywords Cardiac sarcoidosis; Ventricular tachycardia; Adalimumab; Tumour necrosis factor-α inhibitor; Cardiac magnetic resonance; Positron emission tomography-computed tomography

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Introduction

Sarcoidosis is a multisystemic inflammatory disease characterized by non-caseating granulomas.¹ Approximately 2–5% of the sarcoidosis involves the heart and can present as sudden death without preceding symptoms or signs.²,³ Despite the poor prognosis, there is no solid recommendation for pharmacotherapy of cardiac sarcoidosis (CS) in current guidelines. Previous studies showed that corticosteroids and immunosuppressive therapy were often used in patients with CS for controlling inflammation.⁴,⁵ Nevertheless, there were still patients not responsive to steroids or steroid-sparing therapies.⁴ A systematic review indicated that tumour necrosis factor-α (TNF-α) inhibitor was effective for over two-thirds of patients with refractory extracardiac sarcoidosis, with a comparable adverse events, compared with the placebo.⁶ Besides, recent cases and small retrospective studies reported the benefits of TNF-α inhibitors, including adalimumab for patients with refractory CS primarily due to progressive heart failure.⁷,⁸ Although patients with CS and multiple arrhythmias in one body are rare, the optimal treatment remains unknown. In this case report, we present a patient with CS and multiple coexisting arrhythmias who was successfully treated with adalimumab.

Case report

A 45-year-old physical education teacher felt dizziness when playing football 15 months ago, without cough, dyspnoea on exertion, cutaneous abnormal manifestation, or eye pain. At that time, the electrocardiogram (ECG) showed second-degree atrioventricular block (AVB). Then he went to a specialty hospital, where the Holter monitoring showed third-degree AVB and premature ventricular contractions...
(PVCs) (Figure 1A). Cardiac magnetic resonance (CMR) demonstrated inflammation and late gadolinium enhancement (LGE) in right ventricular wall and interventricular septum (Figure 2A,B). The positron emission tomography-computed tomography (PET-CT) revealed multifocal 18F-fluorodeoxyglucose (FDG) uptake in the heart (Figure 3A,B). Ultimately, the endomyocardial biopsy was proven to be CS (Figure 4).

In addition, the patient had a 20-year history of ulcerative colitis presenting with diarrhoea and haematochezia. Although sulfasalazine relieved his symptoms to some extent, he continued to have intermittent diarrhoea and haematochezia, especially after consuming apples, mangoes, sugar cane, and milk. In order to treat CS, he took corticosteroids of 60 mg once daily and mycophenolate mofetil of 1 g twice daily. Eleven months ago, he felt palpitation on the first day when corticosteroids were gradually tapered to 20 mg once daily. The Holter monitor showed first-degree AVB, non-sustained ventricular tachycardia (VT), and frequent PVCs at 4615 beats (Figure 1B). Dosage of corticosteroids was then increased to 60 mg once daily. Ten months ago, corticosteroids were reduced to 55 mg once daily. Nine months ago, he came to our hospital due to palpitation after walking for 2 min. ECG showed atrial flutter and PVCs on admission (Figure 1C).

During his admission, the maximum beats of PVCs and episodes of VT were over 20,000 and nearly 2000 per 24 h, respectively. Detected atrial fibrillation and polymorphic PVCs were shown on Figure 1D,E. CMR demonstrated a mild decrease of LGE (Supporting information, Figure S1). Treatment was then changed to adalimumab once every 2 weeks and corticosteroids 50 mg once daily 8 months ago. One week later, corticosteroids were reduced to 45 mg. However, the patient felt palpitation, dizziness, and fatigue at rest, with sustained VT on ECG (Figure 1F). After taking another 5 mg of corticosteroids and intravenous amiodarone infusion, his sinus rhythm recovered finally. A dual-chamber implantable cardioverter defibrillator was then implanted. He remained on corticosteroids 50 mg once daily for another 1 week and reduced by 5 mg every two to 4 weeks.

Three months after the initial use of adalimumab, corticosteroids were tapered to 35 mg once daily. CMR demonstrated a significant decrease of inflammation and LGE (Figure 2C,D). Holter monitoring showed first-degree AVB.

**Figure 1** Electrocardiographs. (A) Third-degree AVB and PVCs. (B) First-degree AVB and frequent PVCs. (C) Atrial flutter and PVCs. (D) Atrial fibrillation and PVCs. (E) Polymorphic PVCs. (F) Sustained ventricular tachycardia. AVB, atrioventricular block; PVC, premature ventricular contraction.
average PVCs of 500 beats per minute, rare episodes of non-sustained VT, and no atrial tachyarrhythmias. At 6 months following adalimumab initiation, the PET-CT showed a complete resolution of FDG uptake (Figure 3C,D). Corticosteroids were then gradually tapered by 5 mg every 8 weeks. Now, he can teach physical education and walk for 10,000 steps with PVCs of 500 beats every day on corticosteroids of 15 mg once daily. Moreover, after the adalimumab treatment, he no longer experienced diarrhoea or haematochezia, even after eating apples or drinking milk.

Discussion

To the best of our knowledge, we first report an effective treatment of adalimumab for cardiac biopsy-verified CS with multiple arrhythmias including advanced AVB, atrial flutter, atrial fibrillation, PVCs, and VT.

Arrhythmias in patients with CS are challenging to treat. TNF-α promotes the accumulation and activation of macrophages and plays an important role in the formation of non-caseating granulomas.9 TNF-α inhibitors including adalimumab were the options for extracardiac sarcoidosis in those who have not responded to steroids and steroid-sparing agents such as mycophenolate.6 Among patients with refractory CS, recent case reports and retrospective studies showed the benefits of TNF-α inhibitors on changes in cardiac function and corticosteroid dosage.7,8 Besides, a significantly reduced FDG uptake on PET/CT was observed following adalimumab treatment in patients with CS.10–12 However, these studies included patients without cardiac histological diagnosis. In addition, most of these patients presented with progressive heart failure, AVB, or ventricular arrhythmias, rather than multiple coexisting arrhythmias including atrial arrhythmias. To our best knowledge, this is the first case to report the efficacy of adalimumab in a patient with cardiac biopsy-confirmed CS and multiple arrhythmias. With regard to safety, the patient reported no adverse events related to adalimumab during 8 months of the follow-up.

Currently, there is no guideline or census on how to taper corticosteroids when using adalimumab. In this case, tapering corticosteroids by 1 week led to the exaggeration of arrhythmias. Reducing corticosteroids gradually every 2–8 weeks according to symptoms and imaging response seemed effective and safe.

It is worth noting that, consistent with previous studies,13,14 this case observed the remission of ulcerative colitis after adalimumab therapy. This provided additional evidence for the benefits of adalimumab on inflammation control.
Figure 3  $^{18}$F-FDG PET-CT images. The maximum intensity projection PET image revealed high FDG uptake in interventricular septum, right ventricular wall, left atrium, and papillary muscles of the left ventricle before treatment (A). The axial fusion PET-CT image demonstrating hypermetabolic activity in the septum and free wall of the right ventricle before treatment (B). A complete resolution of FDG uptake was seen in the maximum intensity projection PET image (C) and axial fusion PET-CT image (D) after six months of the use of adalimumab. Blue arrows indicated SUV 7.7 consistent with active cardiac sarcoidosis, and green arrows indicated SUV 3.2 consistent with improved cardiac sarcoidosis.

Figure 4 Histological findings of haematoxylin–eosin. Non-caseating granuloma (arrow) and infiltrated inflammatory cells from the right interventricular septum of magnification ×40.
Therefore, in CS patients with multiple arrhythmias who are not responsive to corticosteroids and steroid-sparing agents, adalimumab may be a good alternative to control inflammation and reduce the dose of corticosteroids.

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Conflict of interest

None declared.

References

1. Llanos O, Hamzeh N. Sarcoidosis. Med Clin North Am. 2019; 103: 527–534.
2. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. Lancet. 2014; 383: 1155–1167.
3. Lemay S, Massot M, Philippin F, Belzile D, Turgeon PY, Beaudoin J, Laliberté C, Fortin S, Dion G, Milot J, Trottier M, Gosselin J, Charbonneau É, Birnie DH, Sénéchal M. Ten questions cardiologists should be able to answer about cardiac sarcoidosis: case-based approach and contemporary review. CJC Open. 2021; 3: 532–548.
4. Kandolin R, Lehtonen J, Airaksinen J, Katakkonen K, Tuohinen S, Haataja P, Kerola T, Kokkonen J, Pelkonen M, Pietilä-Effati P, Utrianen S, Kupari M. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. Circulation. 2015; 131: 624–632.
5. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernay CS, Judson MA, Kron J, Mehta D, Coesel Nielsen J, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014; 11: 1305–1323.
6. Adler BL, Wang CJ, Bui TL, Schilperoort HM, Armstrong AW. Anti-tumor necrosis factor agents in sarcoidosis: a systematic review of efficacy and safety. Semin Arthritis Rheum. 2019; 48: 1093–1104.
7. Stevenart J, Le Guenno G, Ruivard M, Rieu V, André M, Grobost V. Case report: TNFα antagonists are an effective therapy in cardiac sarcoidosis. Front Cardiovasc Med. 2021; 8: 676407.
8. Baker MC, Sheth K, Witteles R, Genovese MC, Shoor S, Simard JF. TNF-alpha inhibition for the treatment of cardiac sarcoidosis. Semin Arthritis Rheum. 2020; 50: 546–552.
9. Trivieri MG, Spagnolo P, Birnie D, Liu P, Drake W, Kovačic JC, Baughman R, Fayad ZA, Judson MA. Challenges in cardiac and pulmonary sarcoidosis: JACC state-of-the-art review. J Am Coll Cardiol. 2020; 76: 1878–1901.
10. Rosenthal DG, Parwani P, Murray TO, Petek BJ, Benn BS, De Marco T, Gerstenfeld EP, Jannmohamed M, Klein I, Lee BK, Moss JD, Scheinman MM, Hsia HH, Selvy S, Koth LL, Pampaloni MH, Zikherman J, Vedantham V. Long-term corticosteroid-sparing immunosuppression for cardiac sarcoidosis. J Am Heart Assoc. 2019; 8: e010952.
11. Krishnan M, Cupps TR, Sheikh FH. Tumor necrosis factor-α inhibitor use for treatment of refractory cardiac sarcoidosis in a patient with left ventricular assist device: adalimumab use in refractory sarcoidosis in a patient with left ventricular assist device. J Heart Lung Transplant. 2020; 39: 1504–1505.
12. Miller CT, Sweiss NJ, Lu Y. FDG PET/CT evidence of effective treatment of cardiac sarcoidosis with adalimumab. Clin Nucl Med. 2016; 41: 417–418.
13. Colombel JF, Sandborn WJ, Ghosh S, Wolf DC, Panaccione R, Feagan B, Reinisch W, Robinson AM, Lazar A, Kron M, Huang B, Skup M, Thakkar RB. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: data from ultra 1, 2, and 3. Am J Gastroenterol. 2014; 109: 1771–1780.
14. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D’Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012; 142: 257, e251-253–265.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cardiac magnetic resonance images at six months after initial corticosteroids and mycophenolate mofetil. A mild decrease of late gadolinium enhancement region was showed on short-axis view compared to Figure 2B.