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Cardiac sarcoidosis in an adult person with cystic fibrosis: a case report

Thomas Simon FitzMaurice[1,2], Robert M Cooper[3], Richard Snowdon[3], Monika Arzanauskaite[4,5], Dilip Nazareth[1,2], Martin Walshaw[1,2]

[1]Adult CF Unit, Liverpool Heart and Chest Hospital, Liverpool, UK; [2]University of Liverpool, Liverpool, UK; [3]Department of Cardiology, Liverpool Heart and Chest Hospital, Liverpool, UK; [4]Department of Radiology, Liverpool Heart and Chest Hospital, Liverpool, UK; [5]Cardiovascular Research Center-ICCC, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Abstract. Cardiac sarcoidosis and cystic fibrosis (CF) are both rare conditions and their co-existence has not previously been noted in adults. For the first time we report a case of isolated cardiac sarcoidosis in a woman with CF, and discuss the possible combined aetiological factors. As the life expectancy of people with CF continues to increase, clinicians should be aware of the emergence of concomitant inflammatory conditions typically diagnosed in adulthood, and the diagnostic challenges this may present.

Keywords: ??????

Introduction

CF occurs in 1:2,000 live births and is the commonest life-limiting genetic disease amongst Caucasians (1). Although the gene defect product, an abnormality of the cystic fibrosis transmembrane regulator (CFTR) protein, is expressed in many organs including the heart, disease of the myocardium has not been reported. Sarcoidosis is a chronic granulomatous condition of unknown aetiology with an annual incidence of 7 per 100,000 in the United Kingdom (2). It can cause disease in many body systems, but the heart is only affected clinically in 5% of cases (3). As the lifespan of people with CF continues to improve, the propensity to develop other rare illnesses typically diagnosed in adulthood, such as sarcoidosis, will increase. For the first time, we present a case of cardiac sarcoidosis in an adult person with CF, and discuss the possible combined aetiological factors.

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Correspondence: ???
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Case Report

A 54-year-old Caucasian woman with CF (F508del/R117H), body surface area (BSA) 1.7m^2, presented with chest pain, pre-syncope, and palpitations of several weeks' duration. She had good lung function (FEV_1 70% predicted) and normal pancreatic function, and although chronically infected with *Pseudomonas aeruginosa* had infrequent pulmonary exacerbations. She had no history of cardiac disease, and previously had good exercise tolerance. Chronic medications included ivacaftor, and nebulised colistimethate and rhDNAse.

A 12-lead ECG showed 1st degree heart block and left bundle branch block. Transthoracic echocar-

diography revealed a moderately dilated left ventricle (LV) with spherical remodelling, reduced LV ejection fraction, global hypokinesia, and competent valvular function. E/A ratio was 1.2 and average E/e' ratio 11.7. LV end-diastolic diameter was 59mm. Right ventricular (RV) ventricular basal end-diastolic diameter was 32mm with a tricuspid annular plane systolic excursion of 23mm. Estimated pulmonary artery pressure was within normal limits. Cardiac MRI confirmed impaired LV systolic function with an ejection fraction of 38%, an LV end-diastolic volume index of 117ml/m^2 and global hypokinesia. Pulmonary arteries were of normal calibre. Late gadolinium sequences revealed non-ischaemic mid-epicardial myocardial fibrosis of the septum and inferior RV insertion point fibrosis. There was also near transmural involvement of the anteroseptum in addition to subendocardial RV and subepicardial LV inferior wall extensions, with subtle myocardial oedema (see Figure 1). Maximum basal interventricular septal thickness was 9mm. There was no evidence of fibrotic involvement of the left atrium. A cardiac event recorder showed ventricular ectopic beats (burden 3.4%) and brief non-sustained ventricular tachycardia. A CT of the thorax revealed persistent upper and lower lobe bronchiectasis and mucus plugging consistent with her CF, but no new changes such as lymphadenopathy or perilymphatic nodules.

Serum immunological assays (ANA, ANCA, anti-GBM, ENA, rheumatoid factor), liver function tests, blood cultures and serum virology were unremarkable. Endomyocardial biopsy was culture negative but revealed small, well-defined, non-caseating granulomas surrounded by a limited zone of myocardial scarring, consistent with sarcoidosis. There were no features of systemic sarcoidosis, and no family history of autoimmune disease or sudden cardiac death.

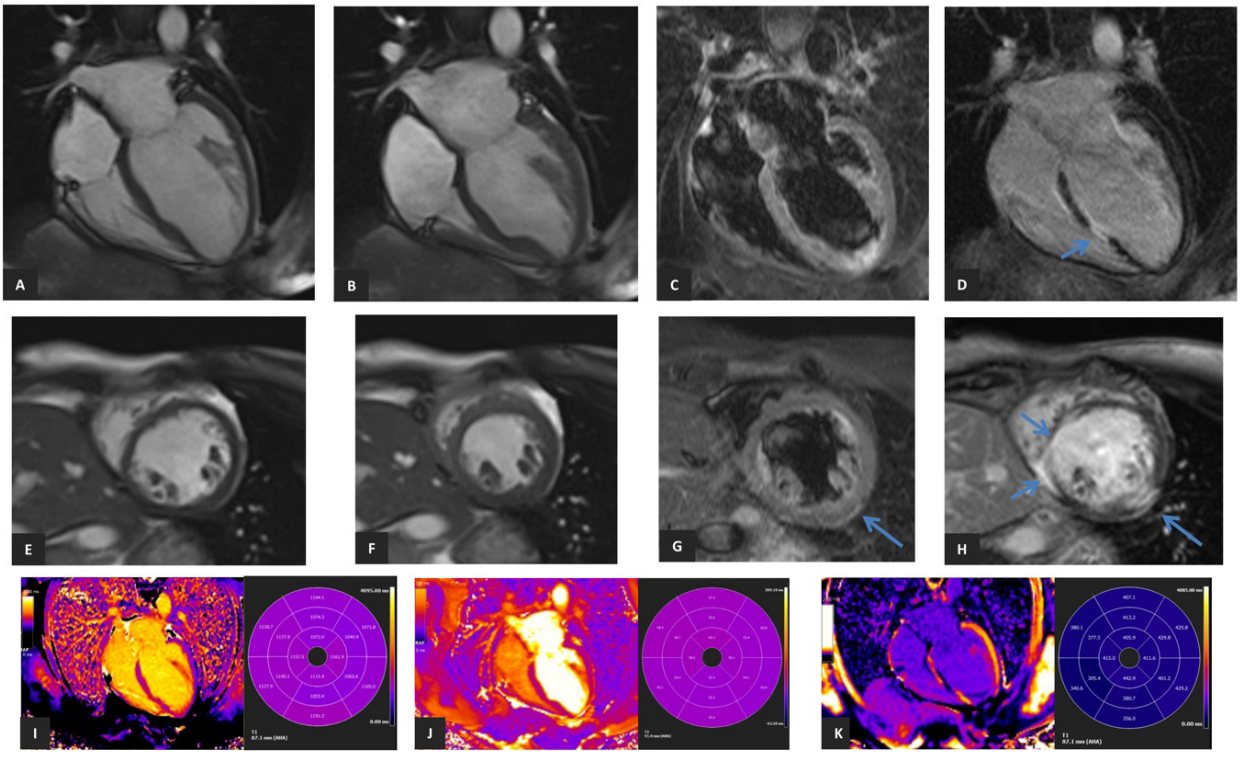

Figure 1. Cardiac MRI study. Top panel: horizontal long axis view in balanced cine SSFP in diastole (A) and systole (B), in T2 STIR (C) and inversion recovery 15' after gadolinium administration (D). Mid panel shows the corresponding images in mid short axis view. Bottom panel: horizontal long axis and corresponding 16 AHA segment polar maps of native T1 mapping (I), native T2 mapping (J) and post-contrast T1 mapping (K). Note the regional wall motion abnormality in the septum (A-B, E-F), foci of subepicardial and mid-wall late gadolinium enhancement (D, H, blue arrows) and subtle subepicardial signal increase in T2 STIR (G, blue arrow). There was diffuse native T1 prolongation with regional shortening after gadolinium administration (I and K, respectively).

Isolated cardiac sarcoidosis leading to non-ischaemic dilated cardiomyopathy was diagnosed with reference to current guidelines (4).

A CRT-D device was inserted during the biopsy procedure. Heart failure medications (bisoprolol, ramipril) were initiated. Immune suppression was initiated with oral corticosteroids (prednisolone 30mg once daily), then weaned to 12.5mg once daily, and methotrexate 7.5mg once daily added. Transthoracic echocardiogram at two months showed improved LV systolic function with an increase in left ventricular ejection fraction to 43%.

Discussion

Cardiac sarcoidosis is most prevalent in middle-aged adults and commonly manifests as heart failure, dyspnoea and conduction abnormalities (5), with a risk of sudden death due to arrhythmia. In most cases extracardiac involvement is also present, but it may occur in isolation in around 25% of cases of cardiac sarcoidosis (6). The presence of myocardial non-caseating granulomas with typical ECG and cardiac MRI changes with no other cause identified satisfied the diagnostic criteria for cardiac sarcoidosis in our patient (7).

There are few reports of sarcoidosis in CF (8, 9), all in childhood or adolescence, and to our knowledge there are none of cardiac sarcoidosis in adults. For the first time, we report a case of cardiac sarcoidosis in an adult with CF. CFTR protein is expressed in most organs, and it has been suggested that the presence of rare missense and splicing CFTR gene mutations may predispose to the development of sarcoidosis (10). However, our patient had more common corrector and minimal function mutations, found in 89.7% and 5.8% of people with CF respectively (1). Both CF and sarcoidosis involve an altered T and B cell immune response, and both conditions are characterised by chronic inflammation. Despite the rarity of the two conditions, these common features raise the possibility that their co-existence was causal. Fibrotic cardiac involvement has been documented in CF (11), although no link has yet been made to sarcoidosis; future studies investigating the prevalence of cardiac sarcoidosis amongst this subset of people with CF may be of interest.

Whilst our case was limited to cardiac involvement, the similarity of symptoms commonly seen in both sarcoidosis and CF (cough, breathlessness, joint involvement) may introduce diagnostic challenges for clinicians, and care should be taken to exclude cardiac sarcoidosis when a diagnosis of CF-related myocardial disease is considered. Although angiotensin converting enzyme (ACE) is commonly raised in the acute phase of sarcoidosis, it may also be elevated in the chronic inflammatory response seen in CF, giving a false positive result. We therefore did not use this test. Given the greater risks of both infection and immunosuppression in people with CF, care should be taken to exclude infective granulomatous disease prior to the initiation of immunosuppression.

The individual in this case was prescribed the cystic fibrosis transmembrane receptor (CFTR) modulator ivacaftor. Combination CFTR modulators have in small studies been shown to reduce QTc interval in at-risk individuals (12), though it is unclear if this had any impact on arrhythmic risk in this case, or whether CF itself has any synergistic effect on arrhythmic risk in cases of cardiac sarcoidosis. The median predicted survival of people with CF in the UK is now over 49 years (1), and is likely to increase with the introduction of CFTR modulator therapy. Physicians should therefore be aware of the possibility of increasing age-related comorbidities in this population, including sarcoidosis, for which diagnosis is most commonly made after age 30. Vigilance for concomitant conditions should be undertaken in those people with CF presenting with breathlessness resistant to standard treatment.

Abbreviation list: ACE: Angiotensin converting enzyme; ANA: Anti-nuclear antibody; ANCA: Anti-neutrophil cytoplasmic antibody; anti-GBM: Anti-glomerular basement membrane (antibody); CRT-D: Cardiac resynchronisation therapy-defibrillator; CF: Cystic fibrosis; CFTR: Cystic fibrosis transmembrane receptor; ECG: Electrocardiogram; ENA: Extractable nuclear antigen; FEV1: Forced expiratory volume [of air] in 1 second; LV: Left ventricle; RV: Right ventricle; UK: United Kingdom

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equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Statement of Ethics: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Care was taken to avoid the inclusion of identifiable details.

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