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High-risk and low prevalence disease: Cardiac sarcoidosis and some of its mimics

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ABSTRACT

In this narrative review of cardiac sarcoidosis, based on a literature search using the terms "cardiac sarcoidosis", "tuberculous myocarditis", "Whipple's disease and myocarditis", and"idiopathic giant cell myocarditis", I have defined cardiac sarcoidosis as a disorder which can be diagnosed either by documentation of the presence of sarcoid-related granulomas in myocardial tissue or by documentation of the association of the presence of sarcoid-related granulomas in extracardiac tissue and symptoms such as complete heart block, ventricular tachyarrhythmia, sudden death or dilated cardiomyopathy which are typical of cardiac sarcoidosis. The differential diagnosis of cardiac sarcoidosis includes granulomatous myocarditis attributable to underlying causes such as such as tuberculosis, Whipple's disease, and idiopathic giant cell myocarditis. Diagnostic pathways for cardiac sarcoidosis include biopsy of cardiac and extracardiac tissue, nuclear magnetic resonance imaging, positron emission tomography, and a diagnostic trial of empiric therapy. Problem areas include differentiation between noncaseating granulomatosis attributable to sarcoidosis versus noncaseating granulomatosis attributable to tuberculosis and whether or not the workup of suspected cardiac sarcoidosis should always include evaluation of biopsy tissue by molecular methods for M tuberculosis DNA as well as by mycobacterium tuberculosis culture. The diagnostic significance of necrotising granulomatosis is also unclear. Evaluation of patients on long term immunotherapy should also take due account of the risk of tuberculosis attributable to the use of tumor necrosis factor-alpha antagonists.

1. Introduction

Sarcoidosis is a potentially treatable, but sometimes fatal, multisystem granulomatous disorder of unknown cause which rarely involves the heart. The incidence of sarcoidosis varies greatly by ethnicity, occurring in 3 to 20 per 100,000 of whites, and 35.5 to 80 per 100,000 of blacks [1]. Cardiac sarcoidosis(CS), in turn, is believed to occur in 5%-10% of patients with known sarcoidosis [2], but this might be a gross underestimate [3]. Notwithstanding its low prevalence, cardiac sarcoidosis is an important cause of sudden death, the latter typically mediated either by the occurrence of complete heart block or ventricular tachyarrhythmia, and, exceptionally, by sarcoidosis-related coronary arteritis. In one series, sudden death was the terminal event in 67% of 89 patients with autopsy confirmation of cardiac sarcoidosis [4]. In a more recent nationwide cohort of 351 Finnish subjects with CS, however, the prevalence of sudden death amounted to 11% [5].

Diagnostic criteria for CS depend on whether histological confirmation of sarcoidosis has been made from an endomyocardial biopsy specimen or from an extracardiac biopsy specimen. This means that some patients will have the diagnosis of CS based on the documentation of noncaseating granulomas in an endomyocardial biopsy specimen, and others will have the diagnosis of CS on the basis of the association of noncaseating granulomas in extracardiac tissue and clinical finding or laboratory findings strongly suggestive of cardiac involvement. Patients who belong to the second category are those who are either not deemed to be candidates for endomyocardial biopsy or those in whom the index of suspicion for CS prevails, and becomes an indication for biopsy of extracardiac tissue, in spite of a nondiagnostic endomyocardial biopsy result. These two sets of criteria and other, more detailed, criteria for CS are enumerated in the Japanese Circulation Society guidelines [6]. Therefore, for practical purposes, there are 2 pathways to a diagnosis of CS:-.

(i)*Histological diagnosis from myocardial tissue.*

OR.

(ii)*Histological documentation of sarcoidosis in extracardiac tissue.*

Patients in the second category are characterised by the association

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of histological diagnosis of extracardiac sarcoidosis and one or more of the following:-.

Unexplained left ventricular systolic dysfunction or corticosteroid responsive cardiomyopathy or heart block, unexplained sustained ventricular tachycardia, late gadolinium enhancement on cardiac resonance imaging in a pattern consistent with CS, patchy uptake on dedicated positron emission tomography in a pattern consistent with CS, positive gallium uptake in a pattern consistent with CS [7]. These criteria apply if causes for those stigmata have been excluded [7].

Cardiac sarcoidosis most commonly involves the myocardium, including the conducting system, hence its predilection for a clinical presentation characterised either by complete heart block(CHB) or sustained ventricular tachycardia(VT) or congestive heart failure(CHF) [5]. In the Finnish cohort of CS, these manifestations had a prevalence of 43%, 13%, and 15%, respectively [5]. Pericarditis, including cardiac tamponade [8], and constrictive pericarditis can also occur [8]. Endocarditis is a much less common manifestation [9]. Exceptionally, granulomatous coronary arteritis may be a manifestation of CS, characterised by the presence of noncaseating granulomata in the media and adventitia of the culprit coronary artery [10].

2. Differential diagnosis of cardiac sarcoidosis (Table 1).

(i)Cardiac tuberculosis features prominently in the differential diagnosis of cardiac sarcoidosis because it is a highly prevalent granulomatous disorder, and can involve the myocardium, giving rise to VT [11,12], CHB [13], sudden death [14,15], and CHF [16,17], respectively. Pericarditis [18], and endocarditis [19], respectively, are also manifestations of cardiac tuberculosis. Exceptionally, coronary arteritis can be a feature of cardiac tuberculosis, characterised by the presence of tuberculosis-related granulomata in the wall of the coronary artery [20]. In the latter example acid fast bacilli were also identified in the vessel wall, and the polymerase chain reaction confirmed the etiopathogenetic role of tuberculosis [20].

Although, on histological examination, the feature which distinguishes a tuberculosis-related granuloma from a sarcoid-related granuloma is the presence of caseation and/or acid fast bacilli in a biopsy specimen that has tuberculosis-related granulomas, acid fast bacilli are not always identifiable, and caseation is not always present. Furthermore, both caseation and acid fast bacilli may be absent from a myocardial biopsy specimen characterised by noncaseating non necrotising granulomas, and in which M tuberculosis DNA is subsequently identified by the polymerase chain reaction(PCR) method [21]. A case has also been reported where the patient had lymph node histology which showed a non-necrotizing and non caseating granuloma in association with positive M tuberculosis culture of lymph node tissue, but a negative PCR test result in the same specimen [22]. Diagnostic confusion between sarcoidosis and tuberculosis is compounded by the fact that some sarcoidosis-related granulomas are characterised by the presence of necrotising inflammation [23,24], a feature more typically associated with tuberculosis [25].

In their study of 93 consecutive patients with hilar/mediastinal lymphadenopathy who were evaluated by transbronchial needle aspiration of lymph node tissue, Senturk et al identified 30 cases with tuberculosis and 63 cases with sarcoidosis. PCR was positive in 17 (56.7%) of the 30 cases of tuberculosis. The combination of PCR and M tuberculosis culture identified 23(60%) of the cases of tuberculosis. Culture on its own identified only 6(20%) of the cases [26]. By contrast, in their evaluation of 11 cases of unexplained VT and 2 cases of unexplained CHF, Mohan et al identified 12 cases in whom M tuberculosis was cultured from biopsy specimens of lymph node tissue. Seven of the 13 patients(including a patient who was culture negative for M tuberculosis), tested positive by PCR [11].

(ii)The differential diagnosis of CS also includes Whipple's disease (WD), the latter a granulomatous disorder that can also involve the myocardium, the pericardium and the endocardium, respectively [27].

Table 1
Differential Diagnosis of Granulomatous Myocarditis.

Parameters	Sarcoidosis	Tuberculosis	Idiopathic Giant Cell Myocarditis	Whipple Disease
Myocarditis	Y	Y	Y	Y
Endocarditis	Y	Y	N	Y
Pericarditis	Y	Y	N	Y
Non caseating granulomas	Y	Y	Y*	Y
Necrotising granulomas	Y	Y	N	N
Caseating granulomas	N	Y	N	N
AFB staining	- ve	+ ve	- ve	- ve
M tuberculosis culture	- ve	+ ve	- ve	- ve
M tuberculosis PCR	- ve	+ ve	- ve	- ve
PAS staining	- ve	- ve	- ve	+ ve
T. Whipple PCR	- ve	- ve	- ve	+ ve
Complete heart block	Y	Y	Y	Y
Ventricular tachy arrhythmia	Y	Y	Y	Y
Congestive heart failure	Y	Y	Y	Y
Sudden death	Y	Y	Y	Y
Coronary arteritis	Y	Y	Y	Y
Lymphadenopathy	Y	Y	N	Y
Increased FDG uptake	Y	Y	Y	Y

Key.
Y = yes N = no.
+ ve = positive result - ve = negative result.
AFB = Acid fast bacilli.
PAS = Periodic acid Schiff.
PCR = Polymerase chain reaction.
FDG = Fluorodeoxyglucose.
* Poorly formed granulomas may occur [38,80].

Superficially, cardiac sarcoidosis is simulated by WD when noncaseating granulomatous lymphadenopathy coexists with myocarditis [28,29], endocarditis [30,31], and constrictive pericarditis [32], respectively. However, the histological hallmark which distinguishes WD is the presence macrophages that have intracellular granules which take up the Periodic Acid-Schiff(PAS) stain [27]. Diagnostic difficulty occurs in WD patients who have granulomas which do not take up the PAS stain [29]. The latter phenomenon was exemplified by a patient with WD-related lymphadenopathy in whom a positron emission tomography study showed increased isotope uptake in the cardiac septa and atria, in a pattern suggestive of an inflammatory process attributable to CS. Biopsy of one of the lymph nodes revealed "a granulomatous lymphadenopathy of the sarcoidosis type, with epitheloid cell granulomas, negative Periodic acid-Schiff stains, and negative] Ziehl Neelsen stains" [29]. The initial diagnosis was sarcoidosis with cardiac involvement. The correct diagnosis of WD was eventually established by polymerase chain reaction evaluation of a duodenal biopsy specimen which was positive for WD [29]. Whipple's disease can also be a cause of congestive heart failure(CHF) and sudden death [33]. In the latter example a 48 year old man had a history of CHF, characterised by left ventricular ejection fraction(LVEF) amounting to 15%, anemia, and weight loss, but no history of diahrroea. A duodenal biopsy specimen was normal. He subsequently experienced an asystolic cardiac arrest from which he could not be resuscitated. Autopsy showed extensive myocardial fibrosis and noncaseating granulomas in the walls of both ventricles. The PAS stain was positive. Further confirmation of WD came from a positive polymerase chain reaction test result [33].

Episodic ventricular fibrillation was the distinctive manifestation of WD-related myocarditis in a 50 year old man who had underlying left ventricular systolic dysfunction characterised by a left ventricular

ejection fraction of 25%. He had concurrent WD-related infective endocarditis characterised by the presence of vegetations on the mitral and on the aortic valve. He responded well to broad spectrum antibiotics and valve replacement surgery [34].

WD-related myocarditis has also been associated with CHB [28]. In the latter example the patient also had intra abdominal lymphadenopathy characterised by sarcoid-like granulomatosis. The diagnostic clue came from histological examination of a small bowel biopsy specimen, which "led to the diagnosis of WD", for which she was prescribed doxycycline. This patient also had coexisting CHF which relentlessly progressed to a fatal outcome. At autopsy histological evaluation of myocardial tissue showed PAS-positive macrophages within foci of myocardial fibrosis. The diagnosis of WD was further confirmed by PCR [28].

Exceptionally, T whipplei can invade the tunica media, adventitia and intima of coronary vasculature. In an autopsy study of 12 cases of WD, both intracellular and extracellular bacilli were found in coronary vasculature. Although most lesions were devoid of inflammation there were some sites which exhibited either florid arteritis or dense scarring [35].

(iii)Idiopathic giant cell myocarditis(IGCM) is the disorder that is most difficult to distinguish from cardiac sarcoidosis. In the Finnish cohort of IGCM, 46% presented with congestive heart failure(CHF), 21% with atrioventricular block, 7% with sustained ventricular tachycardia, and 4% with a syndrome mimicking myocardial infarction [5]. The latter manifestation was also reported by Cooper et al in 4 of their 63 IGCM patients as "a syndrome of chest pain and electrographic findings suggestive of acute myocardial infarction" [36]. More recently, Eizkurtaj et al reported the presence of coronary vasculitis in a patient with IGCM who had died whilst under their care after presenting with rapidly progressive congestive heart failure(CHF). Autopsy revealed small and medium sized coronary arteries that were encompassed by T cell predominant lympho-histiocytic inflammatory infiltrates containing giant cells and dendritic cells [37]. Importantly, in the CHF context, "rapidly progressive HF(heart failure), with or without arrhythmias, that does not respond to usual therapy within 1–2 weeks, warrants consideration of GCM(Giant Cell Myocarditis) [38]. That characterisation notwithstanding, IGCM is, however, also occasionally compatible with a more protracted progression, characterised by transplant-free survival of 5 and 10 years respectively [39].

Histologically, IGCM is typically characterised by diffuse or multifocal inflammatory infiltrates consisting of lymphocytes and multinucleated giant cells. The giant cells are typically associated with eosinophils. Typically, myocyte necrosis is also present [38]. Well organised follicular granulomas containing central giant cells make the diagnosis of IGCM unlikely [40]. The rationale for establishing a distinction between IGCM and CS is that the natural history of IGCM appears to be favourably influenced by multidrug immunosuppression consisting of high-dose corticosteroids in combination with either cyclosporine or tacrolimus [38]. Alternative regimens include the use of mycophenolate mofetil [38]. By contrast, the sole use of corticosteroids is the mainstay of treatment of CS [41].

3. Isolated cardiac sarcoidosis

This is a subtype of CS characterised by absence of extracardiac clinical stigmata of sarcoidosis, concurrently with absence of extracardiac histological manifestations of sarcoidosis. In the absence of a histological diagnosis of extracardiac sarcoidosis, diagnostic criteria specify that "cardiac sarcoidosis cannot be diagnosed even in the presence of cardiac findings suggestive of sarcoidosis, if a histopathological diagnosis by endomyocardial biopsy cannot be made" [42]. Even when endomyocardial biopsy is undertaken, diagnostic difficulty is compounded by the fact that sensitivity of endomyocardial biopsy amounts to only 20%-30%, due to sampling errors attributable to the patchy distribution of sarcoid granulomas in the myocardium [43].

Presenting cardiac features in isolated cardiac sarcoidosis are the same as in multisystem sarcoidosis, namely, conduction defects (including CHB) [44], VT [45,46], aborted sudden death [47], and CHF [48,49], respectively. Among 11 cases of isolated CS evaluated by Tezuka et al, the prevalence of CHB, VT, and LVEF $< 50\%$ amounted to 36.7%, 45.5%, and 81.8%, respectively [50]. Exceptionally, isolated CS may have an electrocardiographic (ECG)presentation characterised by ST segment elevation [51,47]. In one example of isolated CS this phenomenon was attributable to sarcoidosis-related left ventricular aneurysm [51]. In another example of isolated CS ST elevation was attributable to coronary artery vasospasm [47].

Pretest probability of cardiac sarcoidosis is enhanced by a magnetic resonance imaging(MRI) study of the myocardium which documents delayed gadolinium enhancement(DGE). Typically, this occurs in a non coronary artery distribution characterised by a DGE which is preferentially observed in the mid to epicardial layer, whereas, in myocardial infarction, DGE is preferentially observed in the endocardial layer [50,52]. The alternative diagnostic strategy is the use of positron emission tomography(PET) to document areas of high metabolic activity (presumed to be attributable to an inflammatory state) in the myocardium [50,52]. The two strategies are often used concurrently. The presence of CS stigmata on MRI and PET in a patient with stigmata of CS such as paroxysmal VT, for example, is sufficient justification for undertaking endomyocardial biopsy for the purpose of establishing a tissue diagnosis of sarcoidosis [53]. In the latter report of a patient with documented paroxysmal VT, the positive diagnostic yield of endomyocardial biopsy was believed to have been attributable to the fact that the procedure was undertaken under the guidance of cardiac magnetic resonance imaging [53].

4. Empiric treatment as a diagnostic aid: Ambiguities and caveats

When confronted with the dilemma of having to make the distinction between these four granulomatous cardiac disorders(sarcoidosis, tuberculosis, WD, IGCM), and other causes of granulomatous myocarditis [54], in the absence of markers which unequivocally differentiate between them, clinicians sometimes resort to the diagnostic strategy of an empiric therapeutic trial. Although sometimes rewarding, this diagnostic approach is, however, also fraught with caveats and ambiguities as follows:-.

(i)*Treatment-related worsening of CHF following prescription of rifampicin and isoniazid in a patient with suspected tuberculous myocarditis:-*.

This was a patient with had been prescribed antituberculous chemotherapy(pyrazinamide, isoniazid, and rifampicin) on the strength of suggestive chest radiography. One and a half months later he developed congestive heart failure, believed to be attributable to tuberculous myocarditis, and this was associated derangement in liver function tests. In view of hepatic dysfunction, his antituberculous medication was changed to ethambutol, streptomycin, and levofloxacin. When his cardiac status improved, as a result of inotropic support, diuretics and fluid restriction, his liver function tests also improved. Accordingly, he was restarted on rifampicin and isoniazid, and pyrazinamide, this time on the basis of an acid fast bacillus sputum positive result. Within 2 days, thereafter, he relapsed into severe CHF. It was only after corticosteroids had been coprescribed with those three agents that he was able to tolerate antituberculous chemotherapy without experiencing relapse of CHF [55]. Transient paradoxical treatment-related worsening of symptoms and/ or signs of tuberculosis(also entitled "paradoxical upgrading reaction") has also been documented in miliary tuberculosis with neurotuberculosis [56], and in tuberculous lymphadenitis [57], and is believed to be an excessive immune reaction to tuberculoproteins and other cell wall antigens of live or dead mycobacteria [57].

(ii)*Clinical deterioration in spite of empiric treatment with antituberculous chemotherapy as well as corticosteroids:-*.

This was a patient with the association of biventricular cardiac

dysfunction and hilar lymphadenopathy, and in whom lymph node histology showed non caseating granulomatous inflammation that was negative for acid fast bacilli. When he experienced subsequent clinical deterioration, a diagnostic trial of combined antituberculous chemotherapy and high-dose corticosteroids was initiated. Despite these measures he deteriorated and died.. Autopsy showed extensive fibrosis of the right ventricle and patchy fibrosis of the left ventricle. Giant cells were identified within the myocardium. Lymph node tissue tested positive for acid fast bacilli(AFB) using the Ziehl-Neelsen stain [58].

(iii)*Successful outcome from sole use of antituberculous chemotherapy and medication for CHF.*

By contrast there was an excellent response to the combination of full antituberculous chemotherapy(rifampicin, isoniazid, ethambutol, and pyrazinamide) and conventional CHF therapy(diuretics, ramipril and carvedilol) in a 32 year old woman who was sputum positive for AFB, and had symptoms and signs of CHF in association with a pretreatment LVEF of 25%. Her symptomatic improvement was associated with an increase in LVEF to 35% [59].

(iv)*Use of combined corticosteroid and mycophenolate therapy in fulminating cardiac sarcoidosis misdiagnosed as idiopathic giant cell myocarditis:-.*

This was a 56 year old woman with rapidly developing CHF. Endomyocardial biopsy showed a lymphohistiocytic inflammatory infiltrate which included histiocytic giant cells and was consistent with either CS or IGCM. Echocardiography showed left ventricular systolic dysfunction characterised by LVEF amounting to 38%. In view of a fulminating clinical onset consistent with IGCM, she was treated with methylprednisolone as well as mycophenolate mofetil. Due to uncertainty between IGCM and CS repeat endomyocardial biopsy was pursued. This now showed well-formed non-necrotising granulomas with sharp demarcation from adjacent myocardium, findings favouring CS over IGCM. Immunosuppression was therefore changed to prednisone alone, with a plan for outpatient initiation of infliximab. Two months post discharge, echocardiography showed recovery of LVEF to 48% [60].

(v)*Use of corticosteroids and cyclosporine where the distinction between CS and IGCM was blurred:-.*

Decision-making was more complex in the management of a 42 year old African-American man who gave a 2 week history of rapidly progressive effort dyspnoea. Computed tomography showed a significant degree of mediastinal, hilar, and right peridiaphragmatic lymphadenopathy, as well as bilateral multifocal pulmonary consolidation. Left ventricular ejection fraction amounted to 27%. Cardiac magnetic resonance imaging showed a delayed gadolinium hyper enhancement pattern consistent with either IGCM or a severe form of CS. Endomyocardial biopsy, however, showed well-formed noncaseating granulomas, thereby favouring the diagnosis of CS rather than IGCM. Nevertheless, "the first official pathology read was signed out as GCM(Giant Cell Myocarditis)". Accordingly the patient was prescribed prednisone and cyclosporine, in specific treatment of IGCM. He rapidly improved and the LVEF increased to 40%. "Also noted was the interval improvement in the mediastinal lymphadenopathy" [61].

(vi)*Diagnostic trial of empiric corticosteroids in presumed isolated cardiac sarcoidosis without histological proof of sarcoidosis either in cardiac or in extracardiac tissue:-.*

This scenario was exemplified by a 54 year old woman with suspected isolated cardiac sarcoidosis. She had initially presented with CHB necessitating pacemaker implantation. Three years later she developed CHF characterised by LVEF amounting to 29% and brain natriuretic peptide level amounting to 563.5 pg/ml. Gallium scintigraphy was negative, and no evidence of extracardiac sarcoidosis was found. A Fluoro Deoxy Glucose PET(FDG-PET) study, however, showed increased isotope uptake in the myocardial region, thereby enhancing the pretest probability of isolated CS. She refused to have endomyocardial biopsy. Nevertheless, a diagnostic trial of empiric corticosteroid treatment was undertaken. This led to marked improvement in CHF, with consequent reduction in BNP to 179 pg/ml [42].

In the latter example the avid myocardial isotope uptake during the FDG-PET study was correctly interpreted as being attributable to sarcoidosis-related inflammation, thereby justifying a diagnostic trial of empiric immunosuppressive therapy, which proved to be a therapeutic success [42]. The same diagnostic logic was applied to the case reported by Totschnig et al, but without success. In the latter example, the correct diagnosis was WD-related myocarditis instead of sarcoid-related myocarditis [29]. The diagnostic trap was failure to recognise that the increase in the myocardial uptake of isotope in the FDG-PET study was non-specifically attributable to inflammation [50,52] and not specifically attributable to sarcoidosis. In Totschnig et al, as well, diagnostic confusion was compounded by the fact that the lymph node that was evaluated contained noncaseating granulomas, a histological feature which, in that instance, was incorrectly attributed to sarcoidosis [29].

5. Areas of uncertainty

5.1. Necrotizing granulomatosis

This is a subtype of granulomatosis that is common both to tuberculosis and to sarcoidosis. Khurana et al reported the case of a 30 year old man who presented with ventricular tachycardia and mediastinal lymphadenopathy. A lymph node biopsy specimen showed necrotizing granulomas. Ziehl-Neelsen staining identified a few acid fast bacilli, in that lymph node tissue, thereby establishing tuberculosis as the underlying cause of necrotizing granulomatosis [62]. However, in 3 other cases of myocarditis where lymph node histology showed necrotizing granulomas, the diagnosis of a tuberculous etiology was postulated without identification of acid fast bacilli, and without evaluation of lymph node tissue either by PCR or by M tuberculosis culture [63,64,65].

In 4 other examples of necrotizing granulomatosis in whom sarcoidosis was eventually assumed to be the underlying cause, strategies were, however, put in place to rule out tuberculosis, as follows:-.

(i)In two patients reported by McFalls et al an endomyocardial biopsy specimen showed necrotizing granulomatosis but the stain for acid fast bacilli was negative. Culture of the sample for M tuberculosis was also negative. The 2 patients were prescribed prednisone in an initial dose of 60 mg/day. Follow up endomyocardial biopsy showed resolution of the granulomas [66].

(ii)In Miyashita et al a 46 year old woman with a history of uveitis had a computed tomography evaluation which showed mediastinal and hilar lymphadenopathy and hepatosplenomegaly. Lymph node biopsy showed necrotizing granulomatosis. Negative results were obtained from evaluation of lymph node tissue by PCR and by culture for M tuberculosis. Treatment with corticosteroids showed a reduction in mediastinal lymph node size [67].

(iii)Parejo-Moron et al reported 2 patients with lymphadenopathy showing necrotizing granulomatosis.. Both patients initially received standard antituberculous therapy but a lack of response led to a re-evaluation of the diagnostic strategy. In one of the patients lymph node tissue was evaluated by PCR, with negative results. The other patient had a PCR evaluation of tissue obtained from open lung biopsy. Again the results were negative for M tuberculosis DNA. Both patients experienced clinical improvement after corticosteroid therapy [68].

Necrotizing granulomatosis was also reported in a 45 year old patient who appeared to have sarcoidosis coexisting with tuberculosis. He had presented with cervical, mediastinal, and abdominal lymphadenopathy. One of the cervical lymph nodes was characterised by a necrotizing granulomatous reaction, but it tested negative for acid fast bacilli, PCR, and M tuberculosis culture. The Mantoux test was also negative. He did not receive any corticosteroid therapy or antituberculous therapy. Three months later he presented with fever and bilateral pleural effusions. On this occasion he had a Quantiferon test, and this generated a positive test result. Furthermore, culture of a pleural specimen tested positive for M tuberculosis.. He responded well to a

treatment regime comprising both antituberculous chemotherapy and corticosteroids [69].

6. Workup strategy

In view of the fact that tuberculosis is compatible with a tissue biopsy that shows either noncaseating granulomas or necrotizing granulomatosis, should tissue specimens which show either of the two stigmata be routinely evaluated by staining for acid-fast bacilli, culture for M tuberculosis, and also by PCR [11,26]?

Furthermore, in view of increasing awareness of WD as an underlying cause of the same spectrum of cardiac disorders as CS [28,29,30,31,32], and the likelihood that some WD cases might present with granulomatous lymphadenopathy simulating sarcoidosis [28,29,30,31,32], should evaluation of lymph node tissue by PAS stain and by WD-related PCR [70] also be routinely performed in the work up of suspected CS?

Finally, in view of the fact that low diagnostic yield of endomyocardial biopsy is, in part, attributable to patchy myocardial involvement, and its preferential location in the sub epicardial region, should surgical core needle myocardial biopsy (through a left mini thoracotomy) be considered?

Lehtonen et al argued that the latter procedure gives access to areas of myocardium which cannot be reached with a biotome operated from inside the ventricular cavities. Furthermore access via thoracotomy generates an opportunity for visual inspection and palpation of the epicardial surface, thereby helping to target the biopsy to areas of abnormal myocardium. Lehtonen et al provided 3 illustrative examples of myocardial biopsy via mini thoracotomy in which the respective diagnoses were idiopathic giant cell myocarditis(1 case) and cardiac sarcoidosis(2 cases) [71].

7. Acute coronary syndromes in cardiac sarcoidosis and its mimics

Cardiac sarcoidosis can gave a presentation characterised by chest pain, ST segment elevation, and raised serum troponin in spite of absence of coronary artery obstruction on angiography [72]. The 57 year old man in the latter report progressed to fulminating congestive heart failure(CHF), necessitating cardiac transplantation. Histological examination of the explanted heart showed non-caseating granulomas, multinucleated giant cells, and diffuse biventricular fibrosis [72]. The differential diagnosis of that presentation was exemplified by the 25 year old patient who presented with chest pain, ST segment elevation and a serum troponin level of 0.086 mcg/L(normal $<$ 0.03 mcg/L). His subsequent clinical course was complicated by the development of paroxysmal VT and CHF attributable to severe left ventricular systolic dysfunction. Endomyocardial biopsy showed an inflammatory infiltrate composed of lymphocytes, histiocytes, and occasional multinucleated giant cells but no well formed granulomas. A provisional diagnosis of IGCM was made(arguably because there were no well-formed granulomas), and he was prescribed high dose corticosteroids and rabbit antithymocyte globulin. A subsequent computed chest tomography showed subcarinal lymph nodes. Histological examination of a fine needle aspiration specimen showed noncaseating granulomas with absence of acid fast bacilli. The PCR test for M tuberculosis was also negative. Nevertheless, in view of a positive Mantoux test and a family history of tuberculosis, he was started on quadruple antituberculous therapy whilst awaiting the results of culture of the lymph node tissue for M tuberculosis. In due course culture results were positive for M tuberculosis. Repeat endomyocardial biopsy revealed myocardial fibrosis but no active inflammation. Repeat chest computed tomography showed reduction in the size of the mediastinal lymph nodes [73]. Arguably, these observations [72,73] justify inclusion of CS and its mimics in the category of myocardial infarction with non obstructive coronary arteries(MINOCA)[74].

Occlusive coronary artery disease can also be a feature of cardiac sarcoidosis [75]. In one example a 68 year old man presented with acute ST elevation myocardial infarction attributable to occlusion of the left anterior descending(LAD) coronary artery, and this was managed by insertion of a stent. Six years previously he had a diagnosis of submental sarcoidosis-related lymphadenitis for which he was prescribed a 6 weeks course of prednisolone.. Within a month of stent insertion he experienced unstable angina attributable to restenosis in the body of the stent. Multiple recurrences of unstable angina led to a decision to undertake coronary artery bypass surgery. Intraoperatively, a significant inflammatory reaction was noted around the stented LAD artery region. Furthermore, biopsy of the epicardium from the right coronary artery revealed noncaseating granulomatous inflammation which stained negative for acid fast bacilli. Mediastinal lymphadenopathy was also noted. Furthermore, magnetic resonance imaging with gadolinium showed subendocardial hyperenhancement in delayed enhancement images consistent with prior myocardial infarction. Postgadolinium sequences with higher resolution showed thickened coronary arterial walls consistent with coronary vasculitis. Consequently, he was prescribed prednisolone(initially in a dose of 60 mg/day), with the addition of mycophenilate mofetil when the prednisolone dose was reduced to 5 mg/day. The outcome of immunosuppressive treatment was that he experienced no recurrence of unstable angina [75].

Finally, due to the fact that atherosclerotic coronary heart disease is much more prevalent than coronary artery vasculitis, clinicians should be vigilant for the coexistence of clinically significant atherosclerotic coronary heart disease and autoimmune myocarditis [76]. In the latter example a 47 year old man initially presented with an ST elevation inferior myocardial infarct attributable to angiographically documented total occlusion of the right coronary artery. Eighteen months later he experienced another episode of acute myocardial infarction associated with 60% occlusion of the right coronary artery and 80% occlusion of the left anterior descending coronary artery. Incessant ventricular arrhythmia ensued shortly after coronary angiography. Emergency coronary artery bypass surgery was undertaken but he died soon thereafter. Autopsy revealed giant cell myocarditis histologically characterised by numerous giant cells, geographic myocardial necrosis, and absence of granulomas. This coexisted with two-vessel coronary artery disease and posterior myocardial infarction [76].

(iv)*Follow up strategy*.

Bearing in mind the fact that long-term therapy with infliximab is a risk factor for subsequent development of tuberculosis [77], clinicians should be vigilant for the subsequent development of tuberculosis in CS patients treated with long term infliximab.

8. Why is it important for emergency physicians to be aware of CS and some of its mimics?

(i)Complete heart block, ventricular tachyarrythmias and CHF feature prominently in the practice of emergency medicine, and are also the hallmarks of CS and its mimics. Accordingly, screening for CS should be undertaken in patients aged $<$ 60 presenting with unexplained CHB, VT, or cardiomyopathy of unknown cause [6].

(ii)In the absence of electrocardiographic evidence of coronary heart disease as the underlying cause of CHB, VT, or CHF, the work up of patients who have any of those three presenting features should include a search for clinical stigmata of sarcoidosis, and for lymphadenopathy. High-resolution computed tomography of the chest should be the preferred modality for evaluating stigmata of pulmonary sarcoidosis or pulmonary tuberculosis because of its high sensitivity and specificity for detecting pulmonary sarcoidosis [78].

(iii)A fulmination onset of CHF should raise the index of awareness for IGCM, and lend urgency for an optimised workup that includes timely coronary angiography(to rule out coronary artery disease as an underlying cause of fulminating CHF), timely echocardiography(to identify left ventricular dilatation(which is a strong independent

predictor of IGCM-related mortality) [79], and thoracic CT to identify stigmata of either sarcoidosis or tuberculosis.

(iv)When evaluating a patient previously diagnosed as a case of CS emergency physicians should also be aware of the potential for misdiagnosis in the decision-making process for such a diagnosis, and should be aware of the differential diagnosis of CS which, at a bare minimum, should include tuberculous myocarditis, WD-related myocarditis and IGCM.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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