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Case Report

Concomitant symptomatic cardiac sarcoidosis and systemic sclerosis with cardiac involvement: a case report

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Abstract: Sarcoidosis and systemic sclerosis are two inflammatory multisystemic disorders of unknown etiology that may be life-threatening especially when there is cardiac involvement. Both diseases may coexist, however, there are very few case reports of patients with both cardiac sarcoidosis and systemic sclerosis in the literature. We report the case of a 72-year-old female who was initially referred for dyspnea. A chest computed tomography scan showed multiple hilar and mediastinal adenopathy with a non-specific opacity in the middle pulmonary lobe. FDG-PET-scan showed increased FDG uptake in the adenopathy, the middle lobe and the right ventricular free wall. Sarcoidosis was confirmed with a lung biopsy. Both electrocardiogram and echocardiogram were normal. Four months later, the patient developed a high-grade atrioventricular block deemed secondary to her cardiac sarcoidosis. Two years later, the patient was referred to a rheumatologist for severe Raynaud's symptoms, sclerodactyly and acrocyanosis. After thorough investigations, a diagnosis of limited cutaneous systemic sclerosis with systemic and cardiac sarcoidosis was made. This case demonstrates that both cardiac sarcoidosis and systemic sclerosis may coexist. In the literature, either disease may come first. In cases where cardiac symptoms appear after the diagnosis of concomitant sarcoidosis and systemic sclerosis, it might be difficult for clinicians to confirm which disease is responsible for the heart involvement. This is important since early cardiac sarcoidosis treatment should be done to prevent major complications and may well differ from systemic sclerosis treatment. In this review, we discuss the main clinical manifestations and imaging findings seen with cardiac disease secondary to sarcoidosis and systemic sclerosis.

Keywords: Cardiac sarcoidosis, systemic sclerosis, heart failure, atrioventricular block, ventricular arrhythmias

Introduction

Sarcoidosis and systemic sclerosis (SSc) are two inflammatory multisystemic disorders of unknown etiology that can affect the heart [1]. Sarcoidosis is characterized by the formation and accumulation of noncaseating granulomas in several organs such as the lungs, the lymph nodes and the heart. Cardiac sarcoidosis (CS) can be diagnosed using the Heart Rhythm Society (HRS) criteria that include a clinical presentation and confirmation by a biopsy (cardiac or extracardiac), and advanced cardiac imaging, all consistent with CS [2]. Systemic sclerosis is characterized by skin and organ fibrosis as well as vascular dysfunction. The diagnosis is confirmed using the 2013 American College of Rheumatology/European League Against

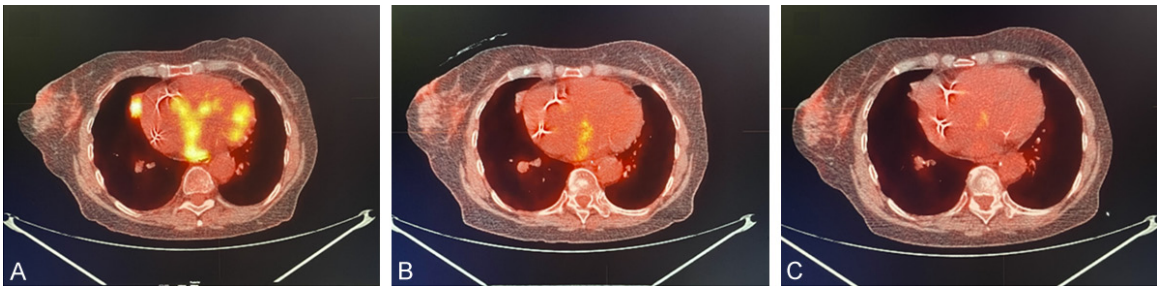

Figure 1. FDG-PET scan before and after immunosuppressive therapy. A. January 2019 before immunosuppressive therapy showing significant patchy FDG uptake especially on the basal septal and lateral walls of the left ventricle (LV) (maximal SUV between 5.1-7.1); B. October 2019 after treatment with methotrexate and prednisone showing significant regression of cardiac hypermetabolic activity but slight persistence of activity on the basal septal wall of the LV (maximal SUV of 2.9); C. June 2020 after increased dose of methotrexate showing complete resolution of cardiac hypermetabolic activity.

Rheumatism Collaborative Initiative criteria [3]. Both diseases can be treated with immunosuppressive therapies with the aim of preventing complications and/or organ dysfunctions.

Similar immunological abnormalities observed in sarcoidosis and autoimmune diseases suggest a possible common and similar physiopathology [4]. Coexistence of sarcoidosis with SSc has been reported in few patients and case reports [4-7]. However, patients with both CS and SSc, such as described in our case report have been rarely reported. Our case report will address the clinical manifestations and imaging findings seen in sarcoidosis and SSc cardiac involvement.

Case report

A 72-year-old female was referred to a pneumologist for progressive dyspnea over the past six months. The patient denied any chest pain, palpitations, lightheadedness or syncope. Chest X ray and CT-scan showed multiple hilar and mediastinal adenopathy up to 2.0 cm with a non-specific opacity of 3.5 × 2.3 × 1.0 cm in the middle lobe. A FDG-PET scan showed multiple hilar, mediastinal and abdominal hypermetabolic adenopathy with a maximal standardized uptake value (SUV) of 6.7. There was also hypermetabolic activity in the middle lobe with a SUV of 4.4 and hypermetabolic activity of the right ventricular free wall suggestive of systemic and cardiac sarcoidosis. Endobronchial ultrasound guided lymph node biopsy was negative. Transthoracic needle biopsy of the middle lobe showed non-necrotizing granulomas and negative Ziehl, Grocott and Periodic Acid Schiff coloration. A diagnosis of systemic sarcoidosis was made.

The patient was referred to a cardiologist for a high suspicion of subclinical CS. The ECG was normal. The transthoracic echocardiogram (TTE) showed a 55% left ventricular ejection fraction (LVEF) and mild pulmonary hypertension (47 mmHg). A cardiac magnetic resonance (CMR) did not show any fibrosis or inflammation. Subclinical cardiac sarcoidosis was suspected by the cardiologist and close follow-up was planned. Four months later, high-grade atrioventricular block was detected and a diagnosis of overt CS was made according to the 2014 HRS criteria [2]. A control FDG-PET-scan showed decreased hypermetabolic activity on the right ventricular free wall compared to the previous exam. A dual chamber implantable cardiac defibrillator (ICD) was implanted but no immunosuppressive therapy was started.

Two years later, a control FDG-PET-scan showed increased patchy myocardial FDG uptake especially on the basal septal and lateral walls of the left ventricle with maximal SUV between 5.1-7.1 (**Figure 1**) as well as many hypermetabolic mediastinal, hilar and abdominal adenopathy consistent with active systemic and CS. The patient was then referred to our CS clinic and methotrexate 15 mg s/c once per week combined with prednisone 40 mg/day was initiated. Prednisone was eventually stopped after a 6 months weaning period. At that time, the patient also reported severe Raynaud's symptoms and acrocyanosis lasting for about six months. The physical exam showed sclerodactyly and multiple telangiectasia on her cheeks,

mouth and hands. She was then referred to a rheumatologist. Capillaroscopy showed giant capillaries and rare tortuous capillaries. Further lab tests showed serum antinuclear antibody at 1/> 2560 (centromere pattern) and 1/160 (speckled pattern). Anti-SSA and anti-centromere were also positive. Hands X-Ray showed calcinosis of her 2nd left finger. A chest CT scan did not show any pulmonary fibrosis. A diagnosis of concomitant pulmonary and cardiac sarcoidosis with limited cutaneous systemic sclerosis was made.

Nine months later, a control FDG-PET-scan showed a significant regression of the overall cardiac hypermetabolic activity with small persistent abnormal basal septal wall activity (SUV of 2.9) (**Figure 1**). Methotrexate was increased to 20 mg s/c once a week. A FDG-PET-scan eight months later did not show any residual cardiac hypermetabolic activity (**Figure 1**). The patient was kept on methotrexate for a total of two years and did not show any relapse of cardiac or extracardiac sarcoidosis (follow-up FDG-PET-scans) even after all immunosuppression was stopped.

Finally, since she had persistent dyspnea and pulmonary hypertension, a right heart catheterization was performed and showed a pulmonary artery pressure of 46/23 mmHg (mean 31 mmHg), wedge pressure of 7 mmHg and pulmonary vascular resistances of 6,35 Woods consistent with a type 1 (precapillary) pulmonary hypertension. The patient was started on Tadalafil at this point.

Discussion

In a recent review, concomitant sarcoidosis and scleroderma have been reported in 35 patients [8] making scleroderma one of the most frequent connective tissue disease associated with sarcoidosis [4]. In the majority of these cases, a diagnosis of diffuse form of SSc was made prior to the diagnosis of pulmonary or systemic sarcoidosis. Of interest, the presence of symptomatic CS with SSc was rarely identified. One may argue that cardiac involvement may be subtle and often not diagnosed or missed and is probably underreported.

Although the exact physiopathology of SSc and sarcoidosis remains unclear, both diseases result from an abnormal immune system activation with a subsequent inflammatory response in some genetically predisposed individuals [6, 9, 10]. In addition, both conditions have demonstrated similarities with regard to environmental factors and cytokines [4, 6]. It is therefore believed that sarcoidosis and SSc are not completely independent from each other and that the association between both diseases does not result from chance alone [4].

Cardiac involvement from SSc has tripled in the last decade and the prevalence of CS has also increased > 20-fold in the last three decades [11, 12]. Cardiac involvement, whether from sarcoidosis or SSc, leads to a worse prognosis [13, 14]. Ekström et al. showed that sudden cardiac death (SCD) is the mode of death in 80% of patients with CS [14]. Tyndall et al. showed that SSc-related cardiac death may be as high as 17% among patients with SSc, although many authors believe SCD may be underestimated in this population [13, 15]. In addition, overt cardiac involvement in SSc is associated with a 70% mortality rate at five years [9]. Screening for cardiac involvement in patients with either disease is strongly recommended [2, 16, 17]. Although only 5% of patients with CS will have clinical manifestations of their cardiac involvement, autopsy studies have demonstrated that myocardial granulomas are present in up to 27% of these patients [1]. Advanced cardiac imaging such as CMR and FDG-PET-scan will show fibrosis and/or edema consistent with cardiac involvement in > 25% of patients with CS [1]. Although the HRS have set criteria for the diagnosis of CS, no such criteria exist for the diagnosis of cardiac involvement from SSc [2]. Therefore, there is a wide heterogeneity in the definition of cardiac involvement from SSc among different studies. An autopsy study of 52 patients with SSc showed that 26 (50%) had myocardial fibrosis of which 23 (44%) had focal randomly distributed fibrosis and normal coronary arteries [18]. A cohort of 201 patients with SSc without known cardiac involvement in which CMR was performed, showed that 53 (26.4%) had a non-ischemic pattern of late gadolinium enhancement (LGE) and 5 (2.5%) had myocardial edema [19]. Another cohort of 150 consecutive patients with SSc in which CMR was performed, demonstrated LGE in 88 (59.9%) and edema in 2 (0.5%) patients [13]. Importantly, 79 (53.4%) patients had cardiovascular symp-

Table 1. Classical cardiac involvement of both cardiac sarcoidosis and systemic sclerosis

	Cardiac Sarcoidosis	Systemic Sclerosis
Clinical presentation	AVB Ventricular arrhythmias/SCD HF	PVC VT
Echocardiogram	Basal septum thinning	Diastolic dysfunction Abnormal GLS
FDG-PET scan	Patchy "heterogenous" FDG uptake anywhere in the heart, but most commonly on LV lateral-basal and septal-basal segments. Diffuse uptake is rare, but can also be seen.	Not well studied. Pilot study from Z. Besenyi et al. showed focal or focal on diffuse myocardial FDG uptake.
CMR	LGE in the LV mid- and subepicardial myocardium of lateral-basal and septal-basal segments.	Diffuse non-ischemic subendocardial LGE. Many other patterns of LGE reported.
Pathology	Non-caseating epithelioid cell granulomas.	Fibrosis with or without foci of inflammation.

AVB, atrioventricular block; FDG, fluorodeoxyglucose; GLS, global longitudinal strain; HF, heart failure; LGE, late gadolinium enhancement; LV, left ventricle; PVC, premature ventricular contraction; SCD, sudden cardiac death; VT, ventricular tachycardia.

toms or events [13]. As for CS, a significant proportion of patients with cardiac involvement from their SSc were asymptomatic.

For those with coexisting sarcoidosis and SSc, it might be very challenging to identify which disease is responsible for the cardiac involvement. The most common initial CS presentation is complete or high-grade AVB occurring before the age of 60-65 years old and is generally associated with the active inflammatory phase of the disease (**Table 1**) [1]. In CS, up to 47% of patients will have AVB as their initial presentation [1]. The classical finding on FDG-PET-scan is a "patchy" heterogeneous FDG uptake by the myocardium with an SUV value > 4.0, especially in the lateral-basal and septal-basal segments of the left ventricle (**Figure 1**) [1]. With immunosuppressive therapy, hypermetabolic activity usually resolves. However, if immunosuppressive therapy is withheld, relapse of hypermetabolic activity may occur at a different site from the previous manifestation. In SSc, conduction abnormalities which result from a fibrotic process are present in about 11% of patients and rarely leads to complete or high-grade AVB [20]. FDG-PET-scan has not been validated in patients with SSc. In one study, FDG-PET-scan was performed in 16 patients with SSc without clinical evidence of cardiac involvement and compared with 9 controls. Eight (50%) patients in the SSc group versus none in the control group showed focal or focal on diffuse myocardial FDG uptake with increased SUV ratio (1.78±0.74 versus 0.98±0.03, $P < 0.05$) and a significantly higher heterogeneity index [21]. More studies are needed to confirm whether FDG-PET-scan has a diagnostic or prognostic value in patients with SSc.

Ventricular tachycardia is the initial presentation in 29% of patients with CS [1]. In SSc, VT and premature ventricular contraction (PVC) occurs in 7-28% and 20-67% of patients respectively [22]. In both CS and SSc, it is critical to search for ventricular arrhythmias with tools such as ECG, Holter or prolonged/continuous monitoring devices since such arrhythmias lead to a worse prognosis [1, 9]. De Luca et al. showed that SSc patients with > 1 190 PVC/24 h had a significant higher risk of life-threatening ventricular arrhythmias [23]. In one study including 10 patients with SSc who had significant PVC or non-sustained VT in which an ICD was implanted, 3 (30%) had appropriate therapies over a 36 months follow-up [24].

In both CS and SSc, ventricular arrhythmias result from reentry circuits through regions of scar [1, 25]. Cardiac magnetic resonance to assess the presence of cardiac fibrosis should be obtained in all patients with suspected CS. It should also be considered in patients with SSc in the presence of an abnormal ECG, echocardiography, or with cardiac symptoms (palpitations, syncope, shortness of breath) [1, 9]. In CS, LGE is mostly seen in the mid- and subepicardial myocardium of the septal and lateral basal segments of the left ventricle [1]. In SSc, CMR classically shows a diffuse non-ischemic subendocardial LGE, although many other patterns have been reported [19, 26]. In both diseases, LGE may be associated with life-threatening ventricular arrhythmias and with a worse prognosis and should prompt monitoring and

Table 2. Red flags that could raise the suspicion of concomitant systemic sclerosis and cardiac sarcoidosis

CS should be suspected in patients with SSc and either	SSc should be suspected in patients with sarcoidosis and either
Complete or high-grade AVB (especially in the absence of fibrosis on CMR) or Unexplained LV dysfunction (especially when associated with prominent adenopathy)	Raynaud's symptoms or Sclerodactyly or Telangiectasia or Calcinosis or Skin thickening or Unexplained pulmonary hypertension

AVB, atrioventricular block; CMR, cardiac magnetic resonance; LV, left ventricle.

search for arrhythmias [13, 19, 27, 28]. Although edema has been reported on CMR in patients with SSc, it is not as common as in patients with CS.

Left ventricular ejection fraction (LVEF) assessed with transthoracic echocardiogram (TTE) is normal in 95% of patients with SSc [29]. However, in patients with CS, heart failure is present in 15-20% of cases [1]. In CS, although infrequent and not pathognomonic, the classical finding on TTE is basal septum thinning due to myocardial scarring [1]. In SSc, although not pathognomonic, the classical finding associated with cardiac involvement is diastolic dysfunction which is found in about 17% of patients and is associated with worse outcomes and increased mortality [30]. Although the predictive value of a decreased global longitudinal strain needs to be assessed in future studies, some authors showed that it may identify subclinical cardiac involvement of SSc and that it may be associated with worse outcomes [31-33]. Right ventricular dysfunction is often reported with SSc but is usually secondary to pulmonary hypertension and does not necessary reflects a direct cardiac involvement from SSc [9].

Cardiologists should consider the possible coexistence of both CS and SSc when a patient presents atypical manifestations or has an unusual clinical course of either CS or SSc (**Table 2**). In patients with SSc, CS should be considered in the presence of complete or high-grade AVB especially when CMR shows the absence of fibrosis with or without myocardial edema. In addition, CS should be suspected in the presence of unexplained left ventricular systolic dysfunction especially when associated with prominent mediastinal/hilar adenopathy. In patients with CS, the presence of Raynaud's symptoms, skin thickening, sclerodactyly or telangiectasia should raise the suspicion for a concomitant SSc and a consultation with a rheumatologist should be considered (**Table 2**). The presence of pulmonary hypertension, although reported with sarcoidosis, should also raise the suspicion of a concomitant SSc.

There are very few data in the literature on the optimal treatment and management of patients with concomitant CS and SSc. We believe that each case mandates an individual approach by a multidisciplinary team.

Of interest, since this case, we have found two more patients with CS and SSc at our CS clinic. Both patients had a favorable outcome with immunosuppressive therapy consisting of prednisone for the first six months and methotrexate. Interestingly, one patient also required mycophenolic acid for the control of his skin thickness related to his SSc reinforcing the idea that the treatment should be tailored to the manifestation of each disease.

Conclusion

Sarcoidosis and SSc are two inflammatory multisystemic disorders of unknown etiology that can affect the heart. Cardiologists and clinicians taking care of these patients should be aware of the possible concomitant occurrence of both diseases. Patients with SSc can develop CS and it should be recognized since worse prognosis and cardiac events can be prevented with appropriate investigation and treatment. Patients with CS may also develop SSc and should be recognized and treated accordingly.

Disclosure of conflict of interest

None.

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