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GRAND ROUND
Heart failure

Cardiac sarcoidosis presenting with complex conduction abnormalities as the first manifestation of widespread systemic sarcoidosis: a case report

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Background Sarcoidosis is a granulomatous multi-organ disease of unknown aetiology. Despite being relatively rare, cardiac sarcoidosis constitutes a very important manifestation of sarcoidosis, as its symptoms regularly precede or occur in isolation of more prevalent ones, and as it is the main driver of mortality in systemic sarcoidosis.

Case summary We present the case of a 37-year-old woman, in which clinically isolated cardiac sarcoidosis revealed widespread systemic sarcoidosis. Apart from constitutional symptoms and strong recurrent dizziness (i.e. near-syncopes), which persisted for multiple years already, our patient initially presented with complex conduction abnormalities, including a right bundle branch block, left anterior hemi-block, and atrioventricular block °1. Following inconclusive endomyocardial biopsies, performed due to detection of focal septal scarring on cardiac magnetic resonance imaging, an ^{18}F-FDG-PET-CT, performed upon admission to our clinic, showed distinct hypermetabolic lesions indicative of active inflammation in various organs and raised suspicion of systemic sarcoidosis. Eventually, histopathological evidence of non-caseating granulomas in affected lymph nodes, extracted by bronchoscopy, confirmed the diagnosis of systemic sarcoidosis after reasonable exclusion of other granulomatous diseases. Immediate initiation of long-term immunosuppressive therapy led to almost complete remission, as monitored by consequential ^{18}F-FDG-PET-CT scans.

Discussion Unexplained complex conduction abnormalities in young patients may be a sign of sarcoidosis, even in isolation of more prevalent symptoms. Correct interpretation and prompt initiation of a structured interdisciplinary diagnostic workup, including ^{18}F-FDG-PET-CT as the imaging modality of choice, are essential to initiate specific treatment and obviate the major risk of mortality resulting from cardiac sarcoidosis.

Keywords Sarcoidosis • Cardiac sarcoidosis • Heart arrhythmia • Cardiac magnetic resonance imaging • Positron emission tomography • Case report

ESC Curriculum 2.1 Imaging modalities • 2.3 Cardiac magnetic resonance • 2.4 Cardiac computed tomography • 2.5 Nuclear techniques • 6.5 Cardiomyopathy

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Learning points

- Complex conduction abnormalities in young patients are highly suspicious of infiltrative cardiomyopathies such as sarcoidosis and constitute an urgent reason to see a specialist.
- Signs of CS may indicate systemic sarcoidosis, even in isolation of more prevalent organ manifestations.
- Biomarkers may be helpful to monitor disease activity but lack sensitivity to be used as screening methods.
- ^{18}F-FDG-PET-CT is a highly informative diagnostic method that should be used in the initial diagnosis and treatment evaluation of sarcoidosis to depict the extent of organ involvement and disease activity, despite exposure to radiation.

Primary specialties involved other than cardiology

(1) Pulmonology
(2) Rheumatology
(3) Infectious Diseases

Introduction

Sarcoidosis constitutes a granulomatous multi-organ disease of unknown aetiology, characterized by the presence of non-caseating granulomas, which may form in virtually any tissue.[1] Pulmonary sarcoidosis (>90%), including mediastinal lymph nodes, is most common, followed by manifestations in the liver (50–80%), eyes (11–83%), skin (25%), and peripheral lymph nodes.[1] Cardiac sarcoidosis (CS), in contrast, is rare.[1] In particular, specialists estimate that only 5% of patients have clinically manifest CS, suggesting a subordinate clinical importance.[1] However, as many as 25% of patients with systemic sarcoidosis feature morphological signs of CS in autopsy studies, indicating that CS may be widely underdiagnosed.[1–3] Additionally, CS is the leading cause of death and CS-specific symptoms regularly precede or occur in isolation of other symptoms in widespread systemic sarcoidosis, placing particular importance on their correct interpretation.[2–4]

Despite recent efforts to simplify the diagnostics, especially of CS, by issuing consensus guidelines,[1,5–7] many clinicians still struggle to identify sarcoidosis patients due to a lack of awareness and experience. Consequently, sarcoidosis is considered underdiagnosed and time from symptom-onset to final diagnosis is long, preventing prompt initiation of effective treatment.[1–3]

Thus, we aim to raise awareness of clinical CS-manifestations and their implications in the interdisciplinary diagnosis of systemic sarcoidosis, using the following exemplary case.

Timeline

2015	Approximate onset of symptoms (reduced physical capacity, dizziness, fatigue, diffuse joint & muscle pain).
2016	First electrocardiographic diagnosis of trifascicular conduction block (right bundle branch block, left anterior hemi-block, and atrioventricular block °1).
April 2019	Exclusion of Lyme-disease through absence of Lyme-specific IgM and IgG antibodies.
May 2019	Cardiac MRI reveals focal septal scarring without signs of active inflammation.
June 2019	Echocardiography reveals impaired left ventricular function and thickened heart walls. Elective myocardial biopsy to clarify septal scarring detected on cardiac MRI. Histopathological diagnosis of inflammatory cardiomyopathy of unknown aetiology.
August 2019	Blood tests unremarkable for CRP, soluble IL-2R, ANA, ANCA. Negative screening for viral infections initiated due to lymphopenia (0.99/nL). Elective implantation of a dual-chamber pacemaker-defibrillator (DDD-ICD. Elective ^{18}F-FDG-PET-CT to evaluate for sarcoidosis demonstrated multiple hypermetabolic lesions compatible with but not evidentiary of sarcoidosis.
September 2019	Bronchoscopy with real-time endobronchial ultrasound-guided transbronchial needle aspiration to obtain samples of suspected sarcoid lesions and bronchoalveolar lavage. Genetic testing negative for Morbus Fabry. Histopathological confirmation of sarcoidosis (i.e. non-caseating granulomas) in obtained biopsies with no signs of malignancy. Microbiologic testing of bronchoalveolar lavage negative for common pathogens causing granulomas (M. tuberculosis, atypical mycobacteria, fungi).
December 2019	After some hesitation by the patient, initiation of immunosuppressive therapy with a combination of prednisolone and cyclophosphamide (cumulative dose: 6000 mg) for a duration of 6 months.
March 2020	Follow-up: Control ^{18}F-FDG-PET-CT showed morphological and metabolic stability of most sarcoid lesions and metabolic normalization of a single pulmonary lesion, indicating partial treatment response.
June 2020	Initiation of immunosuppressive maintenance regimen featuring methotrexate.
September 2020	Follow-up: ^{18}F-FDG-PET-CT indicated good overall treatment response except for splenic lesions.

Case presentation

A 37-year-old white woman presented to our clinic with symptoms, including reduced physical capacity (NYHA II), strong recurrent dizziness (i.e. near-syncope), fatigue, and diffuse arthralgias as well as myalgias, which commenced approximately 4 years prior. Besides recurrent episodes of depression, treated with 60 mg/day fluoxetine p.o., her past

medical history was unremarkable. The patient denied consumption of alcohol, tobacco or drugs. Her family history revealed that her grandfather received a pacemaker at the age of 50, for reasons that could not be further specified. Other familial diseases, including relevant genetic aberrations, were unknown.

Preceding admission to our clinic, an electrocardiogram performed by her cardiologist revealed complex conduction abnormalities, including a right bundle branch block, left anterior hemi-block, and atrioventricular block 1 (*Figure 1A* and *B*). While echocardiographic left ventricular (LV) volume appeared normal, LV-function was mildly impaired (LVEF 51%). Therefore, treatment with *1.25 mg/day Ramipril p.o.* was initiated. Additionally, the interventricular septum was thickened (IVSd 13 mm; LVPWd 10 mm; LVIDd 50 mm). Consecutive cardiac magnetic resonance imaging (CMR), performed due to suspicion of cardiac amyloidosis, unveiled focal septal scarring as possible aetiology of the combined conduction defect, with no signs of active inflammation. Our patient then underwent cardiac catheterization with extraction of four endomyocardial biopsies (EMB) for further diagnostic workup. Histology of those EMBs demonstrated signs of inflammatory cardiomyopathy. In the meantime, negative results for IgG- and IgM-antibodies against *Borrelia burgdorferi* excluded concerns about potential Lyme-disease, following a tick bite 10 years prior.

Upon admission to our clinic, thorough physical examination of our patient revealed no abnormalities. Blood analyses showed elevated NT-proBNP (157 ng/L) but normal levels of high-sensitivity Troponin T (6 ng/L) and Myoglobin (<21 µg/L). Relative (18.3%) and absolute (0.99/nL) lymphocyte count were also abnormally low, implying a possible viral aetiology of the patient's myocardial inflammation. However, a consecutive PCR-screening for cardiotropic viruses proved inconclusive. Biomarkers of rheumatic diseases, suspected due to the patient's diffuse joint and muscular pain, were also inconspicuous (ANA negative; c-ANCA <0.5; *P*-ANCA 1.0). Moreover, levels of soluble Interleukin-2 Receptor (sIL-2R) and serum angiotensin-converting enzyme (ACE), both established biomarkers of sarcoidosis, were normal (383.0 IU/mL and 23.7 U/L, respectively). Additionally, genetic analysis for variants of the α-galactosidase gene, which may cause conduction defects and thickened left ventricular walls by predisposing to Morbus Fabry, were negative.

Despite negative biomarker results, sarcoidosis remained our working diagnosis due to the prevalence of complicated conduction abnormalities in a young patient, histological evidence of inflammatory cardiomyopathy and typical septal scarring in the absence of signs for acute myocarditis on CMR.[1,4,5]

Based on strong suspicion of CS with long-standing complex conduction abnormalities as the most probable cause for our patients recurrent near-syncopes, she underwent implantation of a dual-chamber pacemaker-defibrillator (DDD-ICD) given the risk of ventricular arrhythmias and sudden cardiac death in CS.[4,5] This decision was reached in accordance with indications for device therapy in CS outlined in the HRS expert consensus statement for the management of arrythmias associated with CS published by Birnie *et al.* in 2014 (i.e. '*unexplained near-syncope, felt to be arrhythmic in nature*'; Class IIa) and our patient's wish.[5]

Subsequently, positron emission tomography with ^{18}F-fluorodeoxyglucose integrated with computed tomography (^{18}F-FDG-

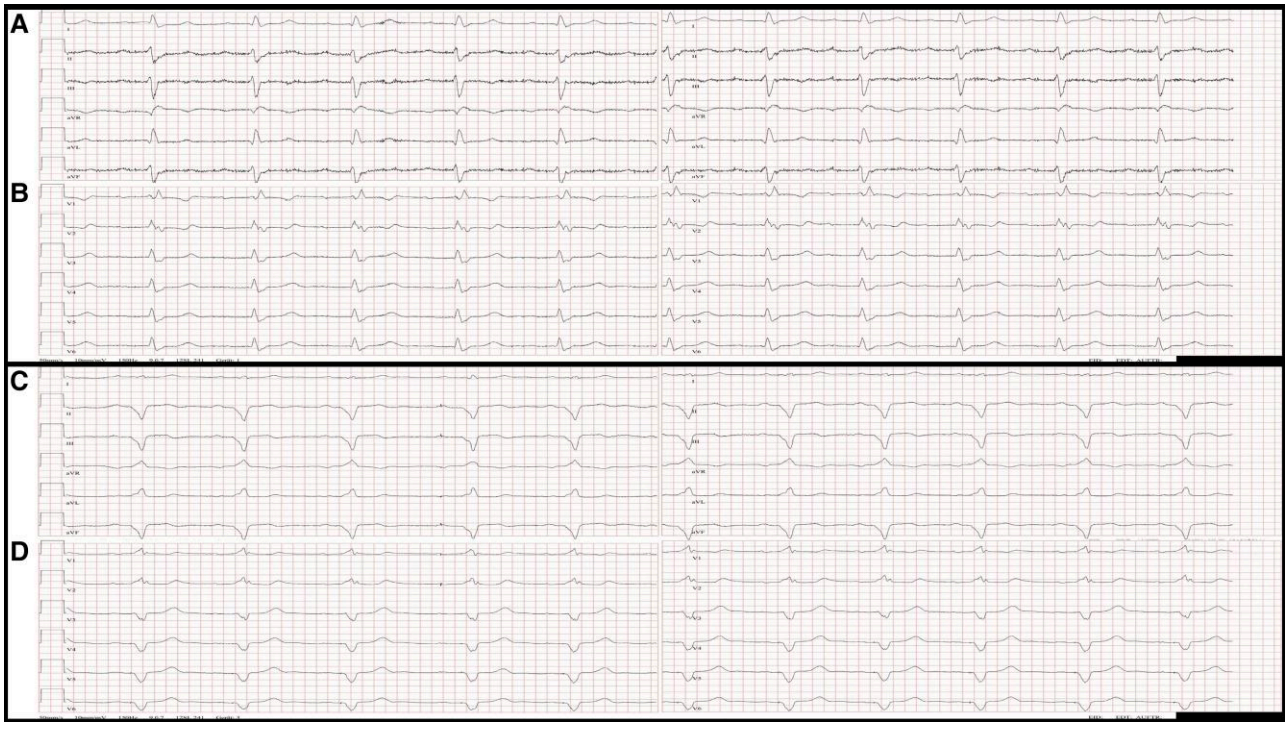

Figure 1 Comparison of electrocardiographic findings at the time of diagnosis (*A*/*B*) and approximately one year after initiation of combined steroid and immunosuppressant therapy (*C*/*D*). Limb (*A*) and precordial leads (*B*) of a 12-lead electrocardiogram at the time of diagnosis showing a normal heart rate (70 b.p.m.), sinus rhythm with first-degree atrioventricular block, right bundle branch block, and left anterior hemi-block. Approximately one year after initiation of combined steroid and immunosuppressant therapy, as well as implantation of a dual-chamber pacemaker-defibrillator, the limb (*C*) and precordial leads (*D*) of a follow-up electrocardiogram show a normal heart rate (67 b.p.m.), sinus rhythm with persistence of the right bundle branch block but recovery of the first-degree atrioventricular block and left anterior hemi-block.

PET-CT) was performed to screen for hypermetabolic lesions, which indicate active inflammation (*Figure 2A, D, G,* and *J*). Our patient followed a special high-fat low-carbohydrate diet to suppress physiological myocardial ^{18}F-FDG uptake. Intense hypermetabolic myocardial lesions were found in the septum, anterior wall, and proximal pulmonary trunk—a pattern indicative of active cardiac sarcoidosis. Moreover, multiple pulmonary, hepatic, splenic, and spinal lesions were found along with various hypermetabolic peripheral lymph nodes.

Although these findings were highly suggestive of systemic sarcoidosis in light of the patient's clinical presentation, co-existent disseminated malignancies (i.e. lymphoma) could not be excluded securely until the diagnosis would be confirmed through biopsy of an easily accessible lesion. Therefore, bronchoscopy with real-time endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed. No signs of malignancy were observed. Two samples of suspicious pulmonary tissue and three samples of ^{18}F-FDG-PET-responsive mediastinal lymph nodes were obtained and sent for histopathological assessment. Additionally, 150 mL of bronchoalveolar lavage (BAL) specimen was extracted and sent for microbiological and cytological examination.

Infections with *Mycobacterium tuberculosis*, other mycobacteria or fungi could be excluded through negative QuantiFERON-tests, cultivation, MOTT-PCR, as well as PAS-stains of the BAL and tissue samples, respectively. Cytological analysis revealed an elevated CD4/CD8 T-cell ratio (4.3), indicative of sarcoidosis. Histopathological evaluation identified characteristic infiltrates with non-caseating epithelioid granulomas in one of the obtained tissue samples. Given the exclusion of other granulomatous diseases, that finding provided sufficient proof of sarcoidosis. Due to the lack of associated symptoms and limited inflammatory activity observed in pulmonary tissue samples, it was concluded that pulmonary sarcoidosis is currently inactive in our patient, while CS prevails. Supporting this conclusion, spirometry results indicated sustained lung function regarding VC (103%), TLC (112%), FEV_1 (80%), FVC (89%), and FEV_1/FVC (91%) with no signs of restriction or obstruction.

Confirmation of sarcoidosis was followed by prompt initiation of immunosuppressive treatment with 50 *mg/day prednisolone p.o.*. A tapering strategy, reducing daily *prednisolone* doses by 10 mg/week until a dose of 20 mg/day was reached and further reductions of 2.5 mg/week after that, was followed to a maintenance dose of 5 mg/day. Additionally, our patient was advised to substitute *vitamin D3* (1000 IE/day) and take pantoprazole (40 mg/day) to reduce the *prednisolone*-related risk of osteoporosis and gastric ulcer.

In consideration of our patient's extensive organ involvement and data indicating significantly reduced relapse rates for combined steroid and immunosuppressive therapy, *prednisolone* therapy was augmented with 1000 *mg cyclophosphamide i.v.,* which was administered once a month for a duration of 6 months in an inpatient setting under gonadal protection through *subcutaneous* administration of *gonadotropin-releasing hormone analogues*.[8] *Cyclophosphamide* was chosen over the more widely used corticosteroid-sparing agent *methotrexate*, based on data from patients with neurosarcoidosis and clinical observations made by the treating team in previous CS patients, indicating superior long-term outcomes.[9] A benefit of *cyclophosphamide* was later also reported by Cacoub and colleagues, who demonstrated significantly lower relapse rates for intravenous *cyclophosphamide* than for *methotrexate* in CS.[10]

The combined immunosuppressive therapy was well-tolerated and induced significant improvements in subjective physical capacity and quality of life within three months of initiation. In contrast, a control ^{18}F-FDG-PET-CT indicated that most sarcoid lesions remained morphologically and metabolically unchanged at that time point (*Figure 2B, E, H,* and *K*). Yet, the therapeutic scheme was retained, as one of the pulmonary lesions appeared to be metabolically normalized, indicating partial response to treatment.

Following six *cyclophosphamide* cycles with a cumulative dose of 6000 *mg*, a maintenance regimen featuring weekly *subcutaneous injections* of 15 *mg methotrexate*, which would facilitate relatively uncomplicated outpatient treatment, was initiated. *Methotrexate* was chosen for therapeutic maintenance to reduce the risk of sterility posed by the well-established cumulative dose-dependent gonadotoxicity of *cyclophosphamide*, since our patient still had a strong wish to have children, as outlined above. Treatment duration could not be finally defined at the time of initiation, as it depends on the course of the disease. Specifically, an approach where the *methotrexate* dose is maintained for at least 6 months upon achievement of remission, followed by a tapering attempt reducing the weekly *methotrexate* dose by 2.5–5 mg every three months, was applied.

Eventually, a second control ^{18}F-FDG-PET-CT performed 9 months after treatment initiation (*Figure 2C, F, I,* and *L*) indicated good overall response with full regression of lymph node and osseous lesions and slight residual activity at most in anteroseptal regions of the heart and in the liver. Solely the splenic lesions remained clearly hypermetabolic. The rate of ventricular stimulation recorded at a pacemaker interrogation approximately 9 months after treatment initiation was still 86%. However, partial recovery of our patient's conduction abnormalities, including the °1 AV-block and left anterior hemi-block, could be noted in an electrocardiographic follow-up approximately one year after initiation of treatment (*Figure 1C* and *D*).

Both pulmonary and cardiac function remained stable throughout the course of treatment, as assessed by serial spirometry and echocardiographic examinations.

Discussion

The case reported above, in which constitutional symptoms (i.e. fatigue) and cardiac features (i.e. complex conduction abnormalities) prevailed in absence of more apparent skin, lung or ocular manifestations despite presence of widespread organ involvement, showcases the diagnostic workup in suspected sarcoidosis and discusses common diagnostic challenges, with particular focus on CS.

Generally, a reliable diagnosis of sarcoidosis requires (a) a compatible clinical picture and/or radiologic features, (b) histopathological evidence of non-caseating epithelioid granulomas, and (c) reasonable exclusion of all conditions resembling sarcoidosis clinically and histologically.[1,5–7]

Due to the variation in organ involvement, a great variety of clinical manifestations are possible in systemic sarcoidosis, as previously summarized in the literature.[1] This manuscript focuses on specific symptoms of CS. Clinically, presenting features of CS range from mild palpitations over pre-syncope or syncope to sudden cardiac death.[1,4–7] Other typical signs of CS include LV-dysfunction and complex conduction system abnormalities.[1,4–7] The latter occur due to formation of cardiac granulomas or consequential granulomatous scars in the septum, where they interfere with electrical conduction along the His-bundle, or ventricular walls, where they create substrate for re-entrant circuits that lead to ventricular arrythmias.[4,11] In particular, atrioventricular blocks, bundle branch blocks, and ventricular tachy-/bradyarrhythmias are common.[4,5] Thus, besides echocardiography, electrocardiography is a useful screening test for sarcoidosis and detection of conduction abnormalities should entail initiation of further diagnostics, especially in young patients (<60 years) with constitutional symptoms and no history of cardiac disease.[1,4]

Where clinical suspicion of sarcoidosis persists, imaging should be considered next. While any imaging modality may detect signs indicative of sarcoidosis, their sensitivity varies drastically. Initial evaluation typically involves chest X-ray, where signs of pulmonary sarcoidosis (i.e. parenchymal infiltration, pulmonary fibrosis) or mediastinal lymph node involvement (i.e. bilateral hilar lymphadenopathy) are visible in approximately 90% of patients.[12]

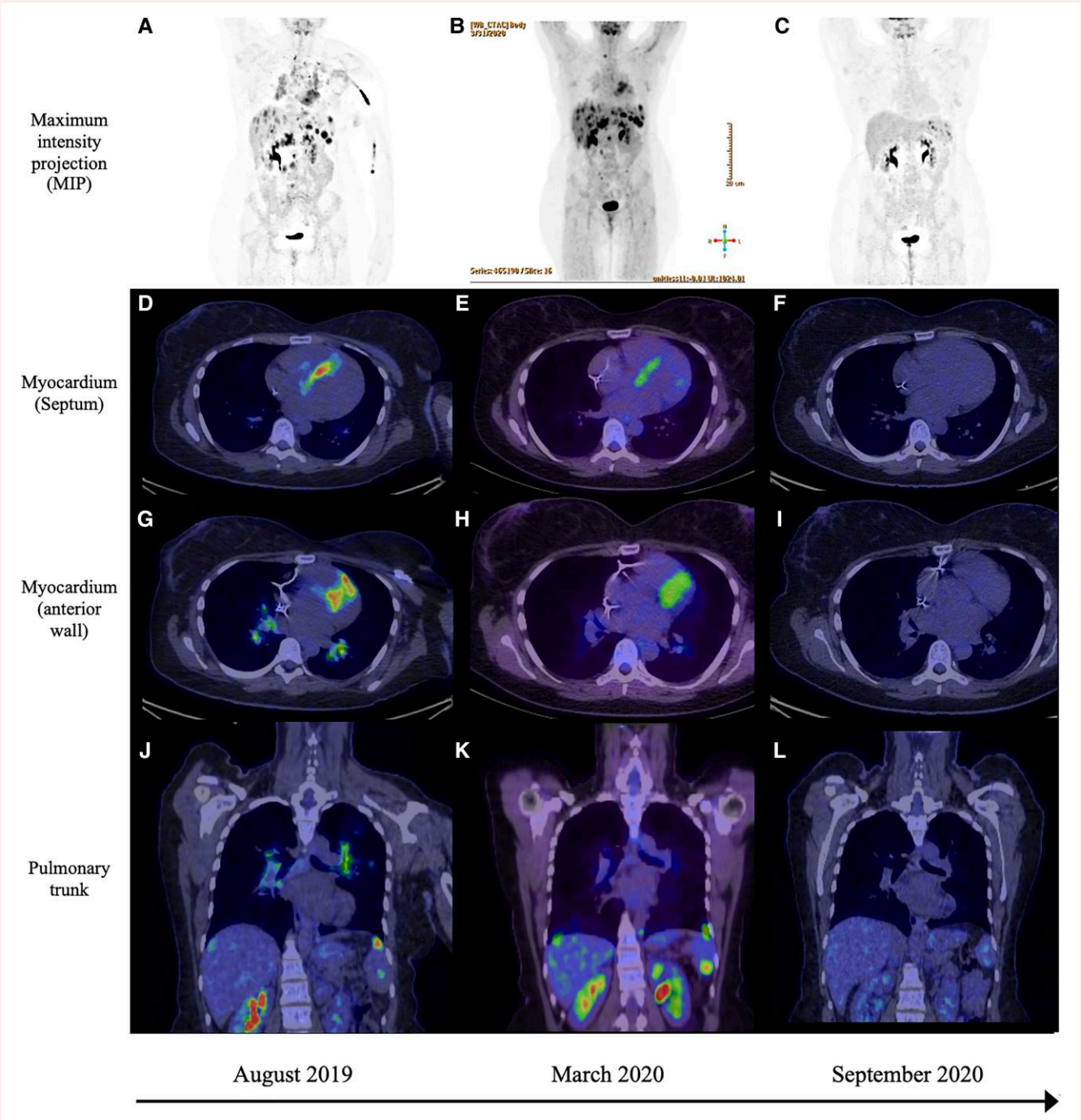

Figure 2 Course of the disease as monitored by sequential ^{18}F-FDG-PET-CT scans. Maximum intensity projection (MIP) images (*A*–*C*) illustrate the overall ^{18}F-FDG uptake of different organs. At time of diagnosis, (*A*) hypermetabolic lesions, showing as darker areas on MIP images, were identified in the myocardium, pulmonary trunk, lung, liver, spleen, various lymph nodes, and the spine. Consequential ^{18}F-FDG-PET-CT scans indicate minimal response to treatment with prednisolone and cyclophosphamide after 4 months (*B*) but an almost full regression after 9 months (*C*). Hypermetabolic myocardial lesions, indicative of cardiac sarcoidosis, were found along the septum (*D*–*F*), as well as the anterior wall of the heart (*G*–*I*) and exhibited a similar response to treatment, with almost full regression reached after 9 months of treatment. In contrast, full regression could be reached after only 4 months of treatment in the hypermetabolic lesions found in proximity to the pulmonary trunk (*J*–*L*).

Detection of extra-pulmonal lesions requires 3D-imaging-techniques, such as magnetic resonance imaging (MRI) or ^{18}F-FDG-PET-CT. With respect to CS, contrast-enhanced CMR can detect scarred myocardial tissue through quantification of late gadolinium enhancement (LGE).[13] Although reliable differentiation between granulomatous scars and scars of other aetiology (i.e. infarction) is impossible, specific patterns may be indicative of sarcoidosis.[13] CMR has great diagnostic validity in CS with sensitivities and specificities of

100% and 78%, respectively.[13] Additionally, the presence of LGE on CMR in CS portends increased risk of mortality and arrhythmogenic events, making it a valuable prognostic predictor.[14] However, one limitation of MRI is that it is not suitable to screen for the involvement of organs other than the heart and central nervous system in widespread systemic sarcoidosis, including identification of affected lymph nodes for potential biopsies. Also, CMR is not able to measure disease activity of sarcoidosis as reliably as ^{18}F-FDG-PET-CT, which makes ^{18}F-FDG-PET-CT the preferred method for measuring treatment response.[15]

^{18}F-FDG-PET-CT detects regions of active inflammation through quantification of excessive ^{18}F-FDG uptake by inflammatory cells, which are geographically allocated by simultaneous CT. Active inflammation on ^{18}F-FDG-PET-CT, like scarred tissue on CMR, is not specific for sarcoidosis and may as well be a sign of lymphoma. Thus, confirmation by biopsy is still required. In the literature, ^{18}F-FDG-PET-CT has been described to be less sensitive (84%) than CMR, while its specificity is slightly higher (83%) in CS.[16] The finding of lower sensitivity of ^{18}F-FDG-PET-CT may result from the fact that centres highly specialized in CMR and cardiac sarcoidosis conducted those studies, which may not reflect every day practice on the broad scale. Based on our experience, we diagnosed numerous patients with cardiac sarcoidosis by performing an ^{18}F-FDG-PET-CT after a CMR missed the diagnosis at an outside clinic or hospital. Several experts in the field of sarcoidosis shared the same experience with us. While this is anecdotal evidence, it would be worthy investigating these observations in a larger cohort as an international multicentre trial. Like CMR, ^{18}F-FDG-PET-CT also bears prognostic value in CS.[17] Additionally, ^{18}F-FDG-PET-CT provides an overview of disease activity and extension in all potentially involved organs and may identify suitable biopsy sites. Therefore, we recommend ^{18}F-FDG-PET-CT over CMR for diagnosis of sarcoidosis. This recommendation is supported by the first randomized controlled trial for treatment of CS, where ^{18}F-FDG-PET-CT was the diagnostic method of choice.[15]

CMR preceded ^{18}F-FDG-PET-CT in our patient due to her strong wish to have children and fears that radiation exposure to approximately 14–17mSv could cause infertility.[18] In comparison, conventional and high-resolution chest CT scans, commonly used to monitor pulmonary sarcoidosis, emit approximately 0.7 and 7.0 mSv, respectively.[19] Hence, a degree of caution is advised but should not restrain clinicians from performing ^{18}F-FDG-PET-CT scans, given the potentially lethal consequences if sarcoidosis missed. Exclusion of pregnancy is compulsory in all females undergoing ^{18}F-FDG-PET-CT. Concerns over radiation could soon be eliminated completely, as combinations of ^{18}F-FDG-PET with CMR, allowing simultaneous detection of both active inflammation and granulomatous scarring, have recently been reported in CS.[20]

Biomarkers, including sIL-2R and ACE, are frequently used due to their apparent ease of use and availability. However, their sensitivity is limited. sIL-2R, a marker of T-cell activation and proliferation, is elevated in >50% of sarcoidosis patients and may correlate with disease activity.[21,22] Yet, its sensitivity (63–82%) and specificity (57–100%) are considered insufficient to be used as sole diagnostic method.[21,22] ACE has been suggested to represent granuloma burden in sarcoidosis and is elevated in 50–70% of patients.[21,22] Similar to sIL-2R, ACE correlates with disease activity, but its reported sensitivity (41–100%) and specificity (83–99%) have been highly inconsistent.[21,22] Thus, biomarkers may be used to monitor disease activity but are not sufficient to diagnose sarcoidosis.[21,22]

Following positive imaging, tissue samples of active (i.e. ^{18}F-FDG-PET-responsive) lesions must be obtained. For that purpose, EBUS-TBNA is the procedure of choice in CS patients with pulmonary and/or lymph node involvement (95%), given its safety and high diagnostic yield.[23,24] Specifically, EBUS-TBNA has a sensitivity around 90% for the detection of non-caseating granulomas without causing serious complications.[24] Additionally, simultaneous retrieval of BAL specimen allows for the necessary exclusion of other granulomatous diseases, as discussed below. In contrast, EMB has a sensitivity of only 19–32%, mainly due to sampling error, and may cause complications in 1–2% of cases.[25,26]

Eventually, histopathological identification of characteristic non-caseating epithelioid granulomas in obtained biopsies consolidates the diagnosis of sarcoidosis.[1] Although accounting for the majority of cells in sarcoid granulomas, epithelioid cells are usually accompanied by multi-nucleated giant cells, which may contain Schaumann or asteroid inclusion bodies.[27] These serve as additional signs of sarcoidosis, despite not being evidentiary.

However, final confirmation of sarcoidosis requires the reasonable exclusion of diseases resembling sarcoidosis clinically and/or histologically, a comprehensive summary of which is provided in one of the available consensus guidelines.[1] Clinical differential diagnoses depend on organ involvement and consequential presentation of individual patients. Generally, infectious diseases should be excluded through viral screening and microbiological testing, especially in patients presenting with fever.[1] Disseminated malignancies may resemble systemic sarcoidosis radiographically and should be excluded.[1] However, various malignancies, such as lymphoma, may also occur concurrently with sarcoidosis or cause sarcoid reactions, preventing secure exclusion even after histopathological examination.[28] Thus, regular follow-ups evaluating the adequacy of chosen treatments are irremissible.

After successful confirmation of CS, especially in those patients with severe conduction abnormalities, the potential need for device therapy to reduce the elevated risk of ventricular arrhythmia and sudden cardiac death in CS should be evaluated.[5,29] In that context, an electrophysiological study, facilitating better assessment of the severity of conduction system disease and further risk-stratification, may be considered as an additional diagnostic step in some CS patients, although its long-term negative-predictive value remains unknown.[5] In particular, an electrophysiological study should be considered for confirmed cases of CS with preserved LVEF, positive LGE on CMR and no existing indications for device therapy.[5]

Specific indications for device therapy in CS are provided in the general 2013 ESC guidelines on cardiac pacing and the complementary HRS expert consensus statement on the diagnosis and management of arrythmias associated with CS.[5,29] As outlined above, our patient was implanted a dual-chamber pacemaker-defibrillator before final confirmation of CS although an explicit indication for device therapy only existed according to the HRS expert consensus statement (i.e. '*unexplained near-syncope, felt to be arrhythmic in nature*'; Class IIa), which is intended to be used for confirmed cases of CS.[5] This was an individual decision based on the strong suspicion of CS that was reached at the request of and after extensive consultation of our patient, who was very concerned about acute severe adverse events. As indicated by the fact that our patient continued to require 86% ventricular stimulation by her pacemaker 9 months after diagnosis, the choice for device implantation was correct in our opinion, although, eventually, partial recovery of our patient's conduction abnormalities could be noted after one year of adequate immunosuppressive therapy (*Figure 1C* and *D*). This is a phenomenon that occurs in almost 50% of cases for AV-nodal conduction abnormalities in CS but remains unpredictable by current means.[5]

Overall, this case illustrates the complexity of the interdisciplinary diagnostic workup and should point out the following considerations in patients with suspected CS who lack more typical symptoms of sarcoidosis:

- Complex conduction abnormalities in young patients are highly suspicious of infiltrative cardiomyopathies such as sarcoidosis and constitute an urgent reason to see a specialist.

- Signs of CS may indicate systemic sarcoidosis, even in isolation of more prevalent organ manifestations.
- Biomarkers may be helpful to monitor disease activity but lack sensitivity to be used as screening methods.
- ^{18}F-FDG-PET-CT is a highly informative diagnostic method that should be used in the initial diagnosis and treatment evaluation of sarcoidosis to depict the extent of organ involvement and disease activity, despite exposure to radiation.

Lead author biography

Maximilian Mueller graduated medicine from Charité – Universtiaetsmedizin Berlin, where he developed a strong interest in cardiology with particular focus on cardiovascular imaging. He is currently working at the CMR unit of the German Heart Center Berlin and is a research fellow at the cardiological department of Charité – Universitaetsmedizin Berlin.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report, including images and associated text, has been obtained from the patient, in accordance with COPE guidelines.

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

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Data availability

The data underlying this article are available in the article and in its online Supplementary material.

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