From trivial to severe arrhythmias: the diagnostic role of multimodality imaging in inflammatory cardiomyopathy through a case series

Christelle Haddad 1,2, Claudia Herrera-Siklody 2, Alessandra Pia Porretta 2, Patrice Carroz 2, Patrizio Pascale 2, and Etienne Pruvot 2*

1National Reference Center for Inherited Arrhythmias of Lyon, Arrhythmias Unit, Louis Pradel Cardiovascular Hospital, Hospices Civils de Lyon, 59 Boulevard Pinel, 69500 Bron, France; and 2Arrhythmias Unit, Department of Cardiology, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, CH-1011 Lausanne, Switzerland

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Background
The diagnosis of inflammatory cardiomyopathy remains challenging in cases presenting with arrhythmia as sole manifestation. An early diagnosis is critical as it may prevent life-threatening complications such as sudden cardiac death and atrioventricular block (AVB). The diagnostic workup of suspected cases includes multimodality imaging that requires an adequate interpretation in order to limit the risk of overdiagnosis.

Case summary
Herein, we report three cases presenting with various new-onset arrhythmias. The first patient was admitted for a third-degree AVB. The second patient suffered from a supraventricular tachycardia which degenerated into ventricular fibrillation. The third case was investigated for symptomatic premature ventricular complexes. No apparent heart disease was observed on standard exams (clinical, biological examinations, and echocardiography). However, cardiac magnetic resonance imaging (MRI) and nuclear imaging (68Ga-DOTATOC and/or 18F-FDG PET/CT) suggested an inflammatory substrate that seemed to correlate with the arrhythmic phenotype. Cardiac inflammation disappeared on immunotherapy for the first case and spontaneously for the third case.

Discussion
These cases emphasize the incremental diagnostic yield of multimodality imaging to highlight myocardial inflammation. Nuclear imaging modalities may complement MRI by enabling the detection of active inflammation. The 18F-FDG PET/CT is well established for the diagnosis of cardiac sarcoidosis but its role remains to be clarified for the diagnosis of myocarditis. An alternative radiotracer, 68Ga-DOTATOC, appears promising by overcoming the main limitation of 18F-FDG but its specificity is not yet well established. The role of functional investigations is discussed as well as the benefit of immunosuppressive treatments.

Keywords
Arrhythmia • Cardiac sarcoidosis • Inflammatory cardiomyopathy • Nuclear imaging • Case series

ESC Curriculum
2.1 Imaging modalities • 6.5 Cardiomyopathy
Introduction

Inflammatory cardiomyopathy (IC) presenting with cardiac arrhythmias as sole manifestation remains largely underdiagnosed. Recent series have found that IC may be the underlying cause of conduction disturbances and ventricular arrhythmias in a significant number of cases. This new awareness is in part due to the progress in complementary exams, especially in multimodality imaging. Herein, we report three cases illustrating the workup that helped diagnose the involvement of IC in several types of arrhythmias.

Timeline

| FIRST PRESENTATION | 3-MONTH FOLLOW UP | 6-MONTH FOLLOW UP |
|--------------------|-------------------|-------------------|
| **Clinical manifestation** | **Standard exams** | **MRI** |
| Syncopal AVB | Normal echocardiography (normal LVEF), normal immunologic and viral exams |
| SVT and VF | LGE | Non-contributory |
| Symptomatic PVC | Diffuse LV uptake (DOTATOC) | Diffuse LV uptake (DOTATOC) |
| | Localized LV uptake (FDG) | Localized LV uptake (FDG) |
| | Non-contributory | Non-contributory |
| **EMB** | Pacemaker implantation | Antiarrhythmic therapy |
| | Immunosuppressive therapy | Wearable cardioverter defibrillator |

Case presentation

**Patient 1**

A 58-year-old man without any medical history was admitted for syncope. The electrocardiogram (ECG) revealed a transient third-degree atrioventricular block (AVB). Apart from that, clinical cardiovascular examination and complementary standard exams (including echocardiography, coronary angiography, and biology) were unremarkable. The ECG, performed after resumption of atrioventricular (AV) conduction (Figure 1A), showed a first-degree AVB associated with a bifascicular block. Immunologic investigations (anti-nuclear antibody, anti-neutrophilic cytoplasmic antibody, and rheumatoid factor) were negative. Serum angiotensin conversion enzyme was within normal range (8.5–25 nmol/mL/min). Viral tests were also negative, which included cytomegalovirus and Epstein–Barr virus antibodies, hepatitis panel, and human immunodeficiency virus screening. Cardiac magnetic resonance imaging (cMRI) revealed mid-wall fibrosis [late gadolinium enhancement (LGE)] involving the base of the interventricular septum but no oedema (Figure 1B). The 18F-FDG PET/CT, however, revealed left ventricular (LV) uptake with a ‘focal on diffuse’ pattern at the base of both the interventricular septum and lateral LV wall suggestive of inflammation without lymph node uptake (Figure 2A). A dual-chamber pacemaker was then implanted and additional investigations were scheduled. Endocardial myocardial biopsies (EMB) from the right ventricle remained non-contributory. The electrophysiological study did not show any ventricular arrhythmia inducibility, but evidenced an abnormal infra-Hisian delay after

**Learning points**

- Inflammatory cardiomyopathy (IC) can manifest as several new-onset arrhythmias without left ventricular function alteration or other systemic manifestation.
- Recent progress in imaging modalities improve the diagnosis of IC thanks to their complementary roles: better sensitivity in identifying active inflammatory activity for nuclear imaging modalities, while magnetic resonance imaging remains the most performant to highlight fibrosis.
- The limited amount of data should be kept in mind as these new promising radiotracers seem to detect other forms of inflammatory process, unrelated to autoimmune disorders.
The conduction disorder was attributed both to fibrosis and inflammation at the base of the interventricular septum. The patient was suspected to suffer from isolated cardiac sarcoidosis, and immunosuppressive therapy (IT) was started thereafter. The active inflammation disappeared on FDG PET/CT (Figure 2B), which was performed 3 months after IT introduction. However, the patient still required intermittent ventricular pacing (20% despite promotion of spontaneous AV conduction).

Patient 2
A 37-year-old man without any relevant medical history was admitted to the emergency department for palpitations. The first ECG revealed a supraventricular tachycardia (Figure 4A). Vagal manoeuvres restored sinus rhythm. Soon after it evolved into a fast, broad, and irregular tachycardia (Figure 4B) suggestive of a pre-excited atrial fibrillation. That degenerated into ventricular fibrillation, which was successfully managed by external defibrillation. The baseline clinical cardiovascular examination was unremarkable, as well as the ECG and echocardiography which were within normal limits (Figure 4C). However, the cMRI revealed mid-wall fibrosis (LGE) affecting the base of the interventricular septum (Figure 4D). There was no basis for toxic, metabolic, or ischaemic causes. The patient was referred for an electrophysiological study, which excluded an accessory pathway. No ventricular tachycardia could be induced at baseline and under isoproterenol infusion. The exam identified an atrioventricular nodal re-entrant tachycardia that was successfully ablated. Due to the fact that 18F-FDG was not available right away at our institution, PET/CT with an alternative radiotracer was performed. This aimed to highlight some potential underlying inflammation that, if present,
Figure 3  (A) Surface (DII, aVF, V1, and V6 leads) and intracardiac electrogram recordings during the electrophysiological study (100 mm/s) pointing out a prolonged HV interval at baseline. (B) Infra-Hisian block: the HV is prolonged to 100 ms after incremental atrial pacing. d, distal; HB, His Bundle; HRA, high right atrium; p, proximal.
would possibly change clinical management. It is noteworthy that $^{68}$Ga-DOTATOC overcomes one of the main limitations of $^{18}$F-FDG. The cardiac physiological uptake of the latter requires a diet poor in carbohydrates to switch cardiac metabolism towards fat consumption. Interestingly, Gallium-DOTATOC imaging suggested a diffuse myocardial inflammation as shown in Figure 5A. Immunological and infectious biological exams were also negative. According to the non-inducibility and a supposedly acute myocarditis, beta-blockers
were initiated and a wearable cardioverter-defibrillator was prescribed for 3 months. During the follow-up, no arrhythmia recurred. Nevertheless, the myocarditis remained active as reported by a positive \(^{18}\)F-FDG PET/CT, which was performed after 6 months (Figure 5B). Consequently, a defibrillator was advised and an IT combining both oral corticosteroids and subcutaneous methotrexate was initiated by the immunologists of our institution. This was in accordance with recent guidelines on the diagnosis and management of isolated cardiac sarcoidosis.

**Diagnostic criteria of isolated cardiac sarcoidosis (JCS 2016)**

**Suspicion of isolated cardiac sarcoidosis**

4 cardiac involvement criteria:
- High AV block or fatal arrhythmia
- LVEF < 50% or focal wall ankylosis
- Basal thinning of the ventricular septum or abnormal wall anatomy (ventricular aneurysm or regional ventricular wall thickening)
- Late gadolinium enhancement on MRI

Myocardial hypermetabolism on \(^{18}\)Ga-Citrate scintigraphy or \(^{18}\)F-FDG PET/CT

- Basal thinning of the ventricular septum or abnormal wall anatomy

1 cardiac involvement criteria

**Clinical diagnosis**:
- Myocardial hypermetabolism on \(^{18}\)Ga-Citrate scintigraphy or \(^{18}\)F-FDG PET/CT
- \(^{18}\)F-FDG PET/CT showing tracer uptake in the region of the left ventricular outflow tract (white arrow) (C) Initial \(^{18}\)F-FDG PET/CT showing tracer uptake in the region of the left ventricular outflow tract (white arrow) (D) \(^{18}\)F-FDG PET/CT at 3 months showing disappearance of the focal uptake.

**Figure 7** Diagnostic criteria for isolated cardiac sarcoidosis according to the latest Japanese Guidelines 2016. AV, atrioventricular; EMB, endomyocardial biopsy; JCS, Japanese Circulation Society; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.
cardiac sarcoidosis.5,6 Despite the persistence of inflammation on nuclear cardiac imaging, the patient remained asymptomatic the following year.

**Patient 3**

A 58-year-old man with a history of stroke was hospitalized to investigate acute-onset dyspnoea and dizziness. There were no obvious signs of heart failure on physical examination. The ECG showed multiple premature ventricular complexes (PVCs) suggesting an origin from the LV summit (Figure 6A).7 Biological findings were unremarkable except for a slight elevation of the erythrocyte sedimentation rate (28 mm/h, normal limit < 10 mm/h). There was no structural heart disease on echocardiogram and on stress cMRI. Due to the fact that 18F-FDG was not available right away, a 68Ga-DOTATOC PET/CT was performed that showed diffuse intense myocardial uptake (Figure 6B). Multiple EMBs were harvested from the right ventricle but they remained non-contributory. The immunologic and viral biological exams, similar to those performed in Patient 1, were also negative. Once available, 18F-FDG PET/CT was performed 3 days after the DOTATOC PET/CT to confirm the suspected inflammation. This exam showed focal uptake within the epicardial fat of the LV outflow tract (Figure 6C) that appeared to match with the origin of the PVC. An inflammatory aetiology was hence diagnosed. The PVC and initial symptoms disappeared spontaneously in a couple of days. Interestingly, clinical reassessment after 3 months showed disappearance of the focal FDG uptake (Figure 6D) and a low PVC burden on Holter recording (1%).

**Discussion**

These three cases illustrate the contribution of inflammation in the genesis of various cardiac arrhythmias. It shows the incremental diagnostic yield of multimodality functional cardiac imaging. Yet, it also emphasizes their limitations and difficult clinical interpretations. The
The role of inflammation as a cause of cardiac arrhythmias is well established as it may damage the conduction system and/or generate the substrate for ventricular arrhythmias. It is noteworthy that brady- or tachyarrhythmias can be the first and only manifestation of myocardial inflammation. A recent prospective study of 107 patients referred for isolated non-ischaemic PVC reported that myocardial inflammation was involved in 51% of the cases. Myocardial inflammation can also manifest as sustained ventricular tachycardia without any systemic manifestation. Regarding conduction disturbances, limited series reported that myocardinis, mainly cardiac sarcoidosis, was discovered in more than 25% of young and middle-aged patients presenting with an unexplained AV block. These observations point out that cardiac inflammation may remain undiagnosed unless actively sought. Regarding the origin of inflammation and in accordance with the latest Japanese Guidelines (Figure 7), isolated cardiac sarcoidosis was clinically highly likely in Patient 1 and suspected in Patient 2. The third patient could have suffered from a transient myocarditis. Alternative forms of cardiac inflammatory diseases could also be suspected. Based on imaging and clinical presentation, some diagnoses can be discarded. None of our patients presented any systemic manifestation of autoimmune diseases known for their cardiac tropism. Giant cell myocarditis often presents as a fulminant disease. Eosinophilic myocarditis usually occurs in a context of chronic hypersensitivity that typically manifests as heart failure or thrombotic complications. Finally, the cause of inflammation was not established with certainty because of the lack of sensitivity of EMBs.

Improvement in the diagnosis of myocardial inflammation is mainly due to progress in cardiac imaging modalities. Cardiac magnetic resonance imaging is well recognized for the screening of myocarditis thanks to the identification of fibrosis and oedema. Nuclear imaging modalities highlight the inflammatory activity using metabolic markers (18F-FDG) or agonists to Somatostatin receptors (SSTR) like 68Ga-DOTATOC. Both functional modalities seem especially promising to diagnose such diseases. Although 18F-FDG PET is not routinely recommended by the Working Group of myocardial and pericardial diseases for the diagnosis of myocarditis, this nuclear imaging technique appears clinically relevant for the workup of suspected cases of sarcoidosis. In a recent meta-analysis, the 18F-FDG PET/CT showed high diagnostic values to detect cardiac involvement in 164 patients suffering from sarcoidosis. All PET/CT performed in our patients demonstrated active inflammation despite the absence of oedema on the cMRI. A small-scale study highlighted the high sensitivity of 18F-FDG (97.5%) but its lack of specificity (38.5%) in diagnosing cardiac sarcoidosis compared to cMRI (75% and 76%, respectively). The combination of both exams has been emphasized in a larger cohort. PET/CT information in addition to cMRI reassessed almost half of the patients with suspected cardiac sarcoidosis. It also demonstrated the presence of cardiac inflammation in two-thirds of patients having LGE on the cMRI. Eventually, a review pointed out the complementary roles of both exams: cMRI is well established to detect fibrosis (reflecting chronic phase), while 18F-FDG PET/CT appears more sensitive to identify early stages of inflammation. Figure 8 is proposing an algorithm that guides physicians throughout the indication and timing of cMRI and 18F-FDG PET/CT exams for patients suspected to suffer from an isolated form of cardiac inflammatory disease (Figure 8). The algorithm recommends starting with cMRI. Whenever there is no oedema and fibrosis, we advocate searching for alternative diagnoses. 18F-FDG PET/CT can still be performed in rare instances of negative cMRI. Oedema without fibrosis is suggestive of an acute myocarditis that may prompt EMBs and viral screening. Fibrosis with or without oedema should lead to 18F-FDG PET/CT. Japanese Circulation Society criteria should then be applied for the diagnosis of isolated cardiac sarcoidosis.

The radiotracer used in our centre, 68Ga-DOTATOC, is reputed for its high affinity to SSTR types 2 and 5, overexpressed by activated macrophages and epithelioid cells such as those present in sarcoid granuloma. It is almost absent in normal myocardium and consequently overcomes the main issue of 18F-FDG, namely its physiological myocardial uptake. Its incremental value in detecting acute cardiac inflammation from cMRI has also been put forward but relies on small-scale studies, which lack strong evidence. SSTR 2 could be overexpressed in other inflammatory processes including vulnerable atherosclerotic plaques. The global myocardial DOTATOC uptake in our third patient with PVCs could reflect some form of endothelial inflammatory process affecting the whole microvascular circulation in a diabetic and smoking patient who recently suffered from a stroke. Furthermore, a recent meta-analysis showed that SSTR 2 radiotracers could display higher diagnostic performances to detect microvascular inflammation than 18F-FDG, which could explain the discrepancy between 68Ga-DOTATOC and 18F-FDG PET/CT in this case. As shown by Lapa et al., an alternative hypothesis is that the local myocardial inflammation triggered a more global inflammation process remote to the damaged area. While a negative test would have been sufficient to prevent further examinations in cases 2 and 3, we felt that confirmation of an underlying potentially life-threatening inflammation by 18F-FDG was mandatory, as other confounding factors might have enhanced 68Ga-DOTATOC uptake. Further studies beyond the scope of these case series are needed to establish the value of 68Ga-DOTATOC vs. 18F-FDG PET/CT in imaging cardiac inflammation.

The prognosis of IC, such as sarcoidosis, is often poorer than that of idiopathic arrhythmias. The efficacy of IT is still debated. It seems beneficial in the early stages of the disease when the LV ejection fraction (LVEF) is preserved, and in cases of AVB. A meta-analysis showed that AV conduction recovered after corticosteroid treatment in nearly half of the patients, while there was no improvement in those who were not treated. With regards to ventricular arrhythmias, data remains limited. A recent prospective study reported a marked reduction in PVC burden and in cardiac inflammation (on imaging) in more than two-thirds of the patients after receiving IT compared to those who were not treated. Despite limited evidence, IT should be initiated before the occurrence of cardiac dysfunction in patients with active IC manifesting as AVB or ventricular arrhythmias. A wait-and-see attitude can be reasonable as long as the prognosis is not affected. In our third case, despite a normal LVEF, a conservative approach appeared justified because of the benign and self-limited arrhythmic presentation of the disease.

In conclusion, IC may be actively sought in patients said to be suffering from ‘idiopathic’ arrhythmias as its clinical manifestation spans the full spectrum of rhythm disorders from PVC to AVB to...
ventricular fibrillation. Affected patients display a poorer prognosis requiring a close follow-up, and, in some cases, IT. Novel nuclear functional imaging modalities appear promising, but data are still limited. Larger-scale studies are needed to clarify their diagnostic and prognostic role.

**Lead author biography**

Christelle Haddad is a cardiac electrophysiologist in the Arrhythmia Unit at the Academic Hospital of Lyon (France). She has worked as a clinical fellow in Lausanne University Hospital (Switzerland) for 1 year in 2020. During this year, she notably gained interest in arrhythmias related to inflammatory cardiomyopathy.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

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

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

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