Inflammatory cardiomyopathy of possibly overlapping aetiology: a case posing treatment dilemma and potential association

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Abstract

We report on a 52-year-old Brazilian immigrant woman with past histories of chronic kidney disease and uveitis, presenting with symptomatic atrioventricular block. Her country of origin being endemic for Trypanosoma cruzi infection, we suspected Chagas disease as the aetiology, diagnosis of which was confirmed by serological tests. Further systemic workup identified an emerging nodular lesion in the lung, which turned out to be a sarcoid epithelioid granuloma on biopsy. Involvement of the kidneys and eyes was suggestive of systemic extension of the lung sarcoidosis. Although imaging modalities did not detect inflammatory foci in the myocardium, the rare coexistence of histologically proven sarcoidosis raised the intriguing concept of cardiac manifestation having arisen from two possibly overlapping aetiologies: Chagas disease and cardiac sarcoidosis. The case highlights a treatment dilemma increasingly likely to be encountered in this globalized world, and also raises the potential, but intriguing, association of these two diseases.

Keywords

Atrioventricular block; Inflammatory cardiomyopathy; Sarcoidosis; Chagas disease; Trypanosoma cruzi; Latin America

Introduction

Pathological features of myocardial cell infiltration, as well as their common arrhythmic manifestations, are the hallmarks of inflammatory cardiomyopathies. The ‘infection-provoked inflammation’, including that caused by Trypanosoma cruzi (Triponoscuta cruzi) parasites in Chagas disease, and the ‘sterile autoinflammation’ seen in cardiac sarcoidosis, are two distinct forms of inflammation leading to a shared arrhythmic condition of the heart.1,2 Accordingly, the treatment approach towards a common cardiac manifestation can vary from targeting the causal pathogen to regulating the autoreacting immune cells. Here, we report on a Brazilian immigrant presenting with symptomatic atrioventricular (AV) block accompanying a Chagas disease diagnosis, who concomitantly developed a lung sarcoïdotic granuloma with possible systemic extension. This rare coexistence not only points to a treatment dilemma, anticipated to be increasingly encountered in this globalized world of exploding immigration, but also raises an intriguing association.

Case report

A 52-year-old Brazilian woman was referred to our cardiology department for assessment of her syncopal episodes. Her first syncope had occurred 2 years earlier, and ever since, she complained of occasional lightheadedness. She lacked any sensation of palpitations, and had not experienced any symptoms or limitations during ordinary activities (New York Heart Association functional Class I). Baseline 12-lead electro-
cardiogram (ECG) showed normal QRS amplitudes and ST-T morphology, and was only remarkable for left anterior hemiblock (Figure 1A). X-ray showed no signs of cardiomegaly or pulmonary congestion. Laboratory examination showed mild elevation in her plasma brain natriuretic peptide level (64.2 pg/dL; reference range <18.4 pg/dL), and a moderately elevated serum creatinine of 1.55 mg/dL, corresponding to an estimated glomerular filtration rate of 28.6 mL/min/1.73 m². Myocardial defects, such as ventricular wall thinning and aneurysms, were absent, and wall motion appeared normal on echocardiographic examination. Telemetry ECG documented no evidence of ventricular tachyarrhythmias but instead revealed a prolonged period of intermittent AV block with 2:1 conduction which, after extensive evaluation, carried the highest probability of being the cause of her symptoms (Fig. 1B).

Given that the patient originated from Brazil, a country endemic for *T. cruzi* infection, and had harboured a positive family history, Chagas cardiomyopathy was sought for as the aetiology. The patient’s serum was tested on multiple serological testing platforms to detect anti-trypanosomal antibodies. The ARCHITECT Chagas assay (Abbott, Chicago, USA) screened ‘positive’ with an enhanced 9.54 signal-to-cut-off index (≥1 signal-to-cutoff index, as threshold for a positive result). Her positive serology was confirmed by two additional immunoassay platforms, namely the Trypanosoma Detect Rapid Test (InBios, Seattle, USA) and the *T. cruzi* IgG CELISA II assay (CELLABS, Sydney, Australia) (Figure 1C,D). While neither the haemoculture nor the genomic amplification by polymerase chain reaction detected persistent parasitemia, the results from serological testing confirmed that she had been chronically infected with *T. cruzi*, meeting the WHO diagnostic criteria for chronic Chagas disease. Her current state, characterized by arrhythmic presentation preceding structural or functional myocardial defects, was suggestive of early stage B1 cardiomyopathy. With a disorder of AV conduction being her sole ECG abnormality, she ranked in the lowest risk category (Rassi score of 0) indicative of 10% 10 year mortality rate.4

Her past histories of chronic kidney disease and granulomatous uveitis prompted further systemic workup. Multiorgan involvement together with slight elevation in the serum lysozyme level (11.8 μg/mL; reference range 5.0–10.0 μg/mL) led to a high suspicion of systemic sarcoidosis. Lung computed tomography revealed an emerging nodular lesion in the right lower lung field, which was absent at the time she underwent a 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) scan 8 months earlier. On biopsy, the nodular lung lesion turned out to be an epithelioid granuloma staining positive for *Propionibacterium acnes* antigens (Figure 2A,B).5 The findings altogether met the criteria for lung sarcoidosis. The co-occurrence of histologi-

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**Figure 1** Clinical findings and the results of *Trypanosoma cruzi* serological testing. (A) The baseline electrocardiogram was remarkable only for left anterior hemiblock. (B) The telemetry electrocardiogram revealed advanced 2:1 atrioventricular block with a ventricular response rate of 33 beats per minute. (C) A lateral flow immunoassay (Trypanosoma Detect Rapid Test; InBios, Seattle, USA) detected a positive band (arrowhead). (D) In the enzyme-linked immunosorbent assay (*T. cruzi* IgG CELISA II; CELLABS, Sydney, Australia), absorbance at 450 nm was measured. Each row indicates negative control (NC), positive control (PC) and the patient’s sample, all measured in duplicates. Samples suggested a positive result.
cally proven, extra-cardiac sarcoidosis brought about the
intriguing concept of her cardiac manifestation having arisen
from two possibly overlapping aetiologies: Chagas disease
and sarcoidosis. Although the index $^{18}$FDG-PET scan lacked
signs of active cardiac inflammation, follow-up scans are
awaited, given that 10% of patients with true cardiac involve-
ment initially return false-negative scans. While the findings
could have given crucial insight into the extent of myocardial
involvement for each aetiology, assessing patterns of late
gadolinium enhancement (LGE) on cardiac magnetic reso-
nance (CMR) imaging was contraindicated due to her ad-
vanced kidney disease.

Since the available trypanocidal drugs lack evidence in
benefiting chronic Chagas disease patients in the long term,
and harbour limited safety profiles regarding their use in
patients with renal impairment, their administration was
suspended. The lung sarcoidosis had never been severe
enough to warrant treatment, but the concomitant
extrapulmonary involvement indicated the need for therapy.
While harbouring the risk of parasitemia reactivation, steroid
therapy was considered in order to target her evident ocular
and renal sarcoidotic manifestations, as well as any poten-
tially masked cardiac extension of the disease. Dosing and
planned duration of therapy are extremely complicated deci-
sions, especially when trypanocidal drugs are contraindi-
cated, as in the present case, and remain yet to be agreed
upon as a trade-off between favourable response and
$T. cruzi$ reactivation. Specific care has been further taken
to minimize the risks of malignant arrhythmic outcome, con-
sidering the arrhythmogenic natures of the two entities. The
patient is now symptom-free after receiving a pacemaker,
and any additional therapy, including an implantable
cardioverter defibrillator, has been withheld on grounds that
she lacks signs of life-threatening ventricular arrhythmia.

**Discussion**

The patient’s clinical picture of inflammatory cardiomyopathy
caused by chronic $T. cruzi$ infection has been complicated by
the histological evidence of an extra-cardiac sarcoidotic gran-
uloma, which evokes the probability of its systemic extension
also involving the heart. The two aetiologies may well overlap
in phenotypic expression while differing in their origins of in-
flammation: from invasion of a parasite to sterile autoreactivity.
Therefore, treatment decisions are at odds from the perspective of the interaction between exogenous factors and host immunity, and a treatment dilemma is
brought about when the two diagnoses may potentially
coexist. If sarcoidosis is to have any contributory role in her
cardiac conduction disorder, the administration of steroids
may be effective in improving the AV block and preventing
future deterioration in cardiac function. In the setting of
Chagas disease; however, the risk of parasitemia reactivation
following steroid therapy poses a challenge in decision
making. Therefore, in such a potentially overlapping
presentation, it becomes essential to specify the
contributory roles of each aetiology in forming the cardiac
conduction abnormality.

Although not performed here due to personal contraindi-
cation issues, CMR can play an active role in this sense. CMR provides information about the spatial distribution of
active inflammation and/or scarring, which aids in differenti-
ating between the triggers of cardiac inflammation. The
LGE pattern seen in Chagas disease resembles that of myocar-
dial ischaemia, involving predominantly the subendocardium.
This is in contrast to the typical LGEs observed in cardiac sar-
coidosis following a non-ischaemic pattern, that is the sparing
of the subendocardium and the localization of enhancement
in the midwall or subepicardium.
Chagas disease, a neglected tropical cardiomyopathy, and cardiac sarcoidosis, a somewhat emerging diagnosis in the present case, may be increasingly faced. Clinical stratification of conduction abnormalities following an inflammatory cardiomyopathy diagnosis thus constitutes a growing agenda.

The case also highlighted an overlooked potential association. Infectious agents, including bacteria, fungi and even viruses, and other exogenous triggers are known causes of granuloma formation in sarcoidosis. While the T lymphocyte-mediated, autoinflammatory reaction leading to granuloma formation in sarcoidosis. However, in this age of increasing globalization, where immigrants from T. cruzi-endemic regions are obtaining better access to advanced medical care, the treatment dilemma seen in the present case may be increasingly faced. Clinical stratification of conduction abnormalities following an inflammatory cardiomyopathy diagnosis thus constitutes a growing agenda.

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Conflict of interest

None declared.

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