JACC: CASE REPORTS VOL. 2, NO. 15, 2020

MINI-FOCUS ISSUE: HEART FAILURE

BEGINNER

CASE REPORT: HEART CARE TEAM/MULTIDISCIPLINARY TEAM LIVE

Chloroquine Cardiotoxicity Leading to Cardiogenic Shock

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ABSTRACT

A patient with a history of heart block and longstanding chloroquine use presented in cardiogenic shock refractory to medical therapy and mechanical circulatory support. Autopsy supported antimalarial-induced cardiomyopathy (AMIC). Progression of AMIC may be halted with early recognition and cessation of antimalarial therapy, highlighting importance of screening and timely diagnosis. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:2381–6)

A 51-year-old female presented to an outside hospital with 2 months of dyspnea, orthopnea, and bilateral lower extremity edema. Her diagnosis was cardiogenic shock. She was initiated on therapy including dobutamine, vasopressors, and diuretics and transferred to the authors' institution for consideration of mechanical circulatory support as a bridge to advanced heart failure therapies.

LEARNING OBJECTIVES

- To understand that new conduction disease, left ventricular hypertrophy, or heart failure in a patient taking antimalarial medications should heighten suspicion for antimalaria-induced cardiomyopathy, a rare, fatal, and underrecognized entity.
- To understand tools for diagnostic evaluation to confirm antimalaria-induced cardiomyopathy, as cessation of antimalarial medications can halt progression of this fatal disease.

She had a history of undifferentiated connective tissue disease and had been taking 250 mg of chloroquine daily for 10 years. One year prior, she underwent dual-chamber pacemaker placement for symptomatic high-grade atrioventricular (AV) block. Echocardiography obtained at that time showed left ventricular ejection fraction (LVEF) >55%.

On arrival, she was tachycardic, lethargic, and volume overloaded, and had cool extremities. Laboratory data (Table 1) demonstrated elevated brain natriuretic peptide (BNP), troponin, and lactate concentrations, with evidence of multiorgan injury and coagulopathy. Right-heart catheterization showed elevated right- and left-sided filling pressures with a cardiac index of 1.8 l/min/m^2 and mixed venous saturation of 29%.

WHY MIGHT THIS PATIENT BE AT RISK FOR CARDIOMYOPATHY?

First, she had a 13-year history of rheumatic disease, which is associated with endothelial dysfunction and

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 6, 2020; revised manuscript received September 28, 2020, accepted September 29, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.09.044

ABBREVIATIONS AND ACRONYMS

AM = antimalarial medication

AMIC = antimalaria-induced cardiomyopathy

AV = atrioventricular

BNP = brain natriuretic peptide

CMR = cardiac magnetic resonance

EMB = endomyocardial biopsy

LV = left ventricular

LVEF = left ventricular ejection fraction

higher risk of coronary atherosclerotic-associated events and heart failure, driven by fibrosis or systemic and vascular inflammation (1). Although disease-modifying antirheumatic drugs treat primary rheumatic complications, they are not known to reduce risk of long-term cardiovascular disease (1). Antimalarial medications (AM), including chloroquine and hydroxychloroquine, are commonly used for immune-modulating effects and can result in long-term cardiotoxicity in the form of an infiltrative cardiomyopathy known as antimalarial-induced cardiomyopathy (AMIC) (2).

Second, this patient developed AV block at age 50 years. Generally, AV block is a rare phenomenon, but the incidence increases with age. Its presence, particularly in younger patients (adults <60 years of age), should prompt a thorough search for reversible causes (3). Finally, patients who require right ventricular pacing may be at risk for pacing-induced cardiomyopathy with deterioration of LV function.

WHAT WAS THE INITIAL DIFFERENTIAL DIAGNOSIS AND EVALUATION FOR THIS PATIENT'S CARDIOGENIC SHOCK?

The differential includes ischemia, fulminant myocarditis, stress-induced cardiomyopathy, severe valvular disease, restrictive/infiltrative cardiomyopathy, progression of an underlying cardiomyopathy related to her autoimmune disease, and AMIC. Electrocardiography and echocardiography are first-line tests for evaluation.

Electrocardiography showed an atrial-sensed ventricular-paced rhythm (**Figure 1**). Pacemaker interrogation revealed an increased ventricular pacing burden for 3 months. Echocardiography showed increased LV wall thickness and severe biventricular systolic dysfunction with global hypokinesis (Video 1).

The patient's history, presentation, and echocardiographic results were not consistent with ischemic, valvular, or stress cardiomyopathies. Autoimmune laboratory panel results were normal (**Table 1**). She had no family history of cardiomyopathy, making inherited cardiomyopathies less likely. Her history of AV block and increased ventricular wall thickness suggested an infiltrative cardiomyopathy such as AMIC, Fabry disease, or amyloidosis rather than pacing-induced cardiomyopathy. She had normal serum-free light chains (**Table 1**), and her age, white race, and female sex made transthyretin amyloid unlikely. AMIC was suspected, given long-term exposure to chloroquine. In published case series, AMIC is diagnosed with endomyocardial biopsy (EMB), which was considered the next step (4).

WHAT WAS THE ROLE OF EMB IN THIS CASE?

Guidelines suggest that an EMB should be performed in patients with rapidly progressive heart failure, ventricular dysfunction, or malignant arrhythmias, or when there is high clinical suspicion for a diagnosis that requires histology (5). EMB is recommended for AV block if the block develops in conjunction with new heart failure, such as cardiac sarcoidosis, infiltrative cardiomyopathies, or myocarditis, which can all manifest with AV block. In stable patients, an EMB can be pursued if noninvasive tests (imaging or genetic testing) are nondiagnostic (5). Unfortunately, this patient's thrombocytopenia (thought to be due to underproduction in the setting of critical illness) and hemodynamic instability prohibited EMB.

IS THERE A ROLE FOR CMR?

Cardiac magnetic resonance (CMR) is an appropriate test for evaluation of suspected acquired cardiomyopathy (6). In addition to functional and morphological assessment, CMR with gadolinium allows for tissue-level characterization of scar patterns by late gadolinium enhancement and quantification of edema (T2 mapping), fibrosis (T1 mapping), and expansion of the extracellular volume. A characteristic combination of these features can be diagnostic in the correct clinical context (7). Thus, for certain cardiomyopathies, CMR can be used as an alternative to EMB. It remains unproven whether CMR can conclusively diagnose AMIC, but it may exclude other diagnoses.

The advent of wideband techniques and specific shimming algorithms to reduce artifacts allows for improved image quality in patients with pacemakers and defibrillators (7,8). Although the present patient's pacemaker was compatible with CMR, her hemodynamic instability precluded CMR. Chloroquine was stopped empirically given high suspicion for AMIC.

WHAT ARE THE CLINICAL FEATURES OF AMIC?

AMIC is a rare, underrecognized, and fatal cause of cardiomyopathy due to lysosomal enzyme dysfunction provoked by AM drugs, leading to accumulation of phospholipids and glycogen with cardiomyocyte

vacuolization (2). In the largest systematic review of AMIC cases (127 patients), the cardiac manifestations included conduction disorders (85%), heart failure (26.8%), LV hypertrophy (22%), LV hypokinesis (9.4%), valvular dysfunction (7.1%), and pulmonary arterial hypertension (3.9%), with 10.3% of subjects undergoing pacemaker placement (9). Patients' conditions were diagnosed by CMR, EMB, or skeletal muscle biopsies. Median duration of treatment in AMIC patients was 7 years for chloroquine and 8 years for hydroxychloroquine, with median cumulative doses of 803 g and 1,235 g, respectively, although with substantial variability in both duration and dosage. The mortality rate was 31% in this particular series; however, with cessation of AM, cardiac function recovered in 45%. Heart transplantation was performed in 2 patients whose LVEF did not recover after AM withdrawal (9). In another series, the mortality rate was even higher at 45% with death occurring at mean 3.3 ± 4.2 months after diagnosis (4).

Diagnosis of AMIC can be elusive, as clinical presentation is highly variable, ranging from preserved to reduced systolic function, including dilated (rare) to restrictive forms (4). Aside from ventricular wall thickening, features of AMIC on CMR or other imaging modalities have not been consistently described in the medical literature, nor are they necessarily diagnostic. In 1 review of biopsy-proven AMIC, CMR findings were reported in 12 cases: LV hypertrophy was detected in 83.3%, right ventricular hypertrophy in 50%, and late gadolinium enhancement in 58%, most commonly with a patchy, nonvascular pattern in the septum or lateral wall of the LV (4).

WHAT WAS THE MANAGEMENT OF THIS PATIENT'S CARDIOGENIC SHOCK?

Despite cessation of chloroquine and inotropic and intra-aortic balloon pump support, the patient deteriorated. Given severe right heart and multiorgan failure, she was not a candidate for an LV assist device or transplantation as a durable exit strategies and was placed on venoarterial extracorporeal membrane oxygenation as a bridge to recovery. Unfortunately, she remained in refractory shock. Comfort measures were pursued, and she died.

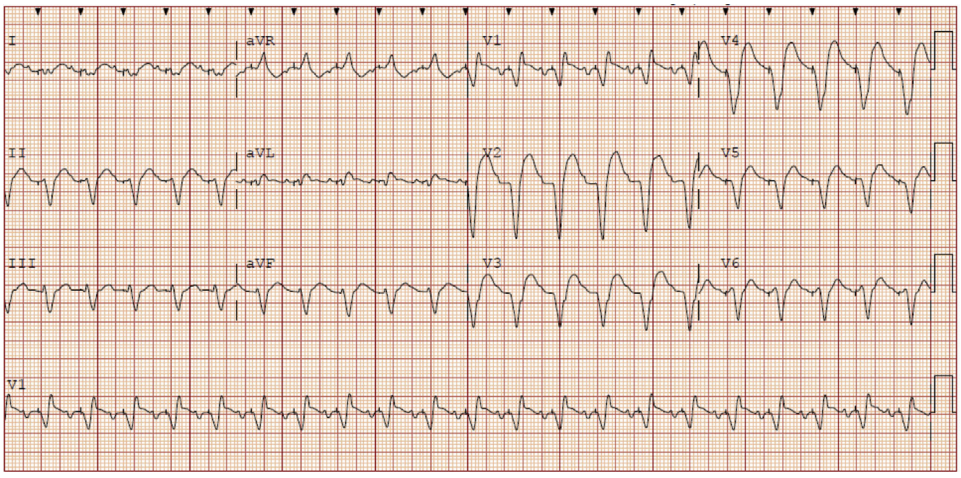
Diagnosis of AMIC was supported histologically at autopsy, which revealed characteristic features (**Figures 2A to 2E**). Although vacuolar myopathy may be found in other conditions such as dermatomyositis

TABLE 1 Presenting Laboratory Tests and Their Values

Serum chemistry	
Sodium	131 mmol/l
Potassium	4.8 mmol/l
Chloride	100 mmol/l
Carbon dioxide	13 mmol/l
Blood urea nitrogen	62 mg/dl
Creatinine	2.36 mg/dl
Lactate	4.1 mmol/l
Serum blood count	
White blood cells	6.1×10^3 cells/μl
Hemoglobin	8.9 g/dl
Hematocrit	28%
Platelets	25×10^3 cells/μl
Coagulation	
International normalized ratio	2.5
PTT	48.0 s
Fibrinogen	116 mg/dl
ADAMSTS13 level	29%
Cardiac biomarkers	
Brain natriuretic peptide	14,773 pg/ml
Troponin-1	5.46 ng/ml (ref. ≤0.03 ng/ml)
Autoimmune panel	
Anti-Jo-1 (histidyl-tRNA synthetase) antibody	0
Anti-RNP (U1) antibody	0
Anti-EJ (glycyl-tRNA synthetase) antibody	Negative
Anti-Ku antibody	Negative
Anti-Mi-2 (nuclear helicase protein) antibody	Negative
Anti-OJ (isoleucyl-tRNA synthetase) antibody	Negative
Anti-P155/140 antibody	Negative
Anti-PL-12 (alanyl-tRNA synthetase) antibody	Negative
Anti-PL-7 (threonyl-tRNA synthetase) antibody	Negative
Anti-SRP antibody	Negative
Anti-U2 small nuclear RNP antibody	Negative
Anti-SSA 52 (Ro) antibody	1
Anti-SSA 60 (Ro) antibody	5
Anti-PM/Scl 100 antibody	Negative
Anti-fibrillarin (U3 RNP) antibody	Negative
Anti-SAE1 (SUMO-activating enzyme) antibody	Negative
Anti-NXP2 antibody	Negative
Anti-MDA5 (CADM-140) antibody	Negative
Anti-TIF1 gamma (155 kDa) antibody	Negative
Serum protein electrophoresis	
Protein, total	4.8 g/dl
Albumin serum protein electrophoresis	2.9 g/dl
Alpha 1 globulin	0.2 g/dl
Alpha 2 globulin	0.5 g/dl
Beta globulin	0.6 g/dl
Gamma globulin	0.6 g/dl
Serum immunofixation	No monoclonal immunoglobulin detected

CADM = clinically amyopathic dermatomyositis; *MDA* = melanoma differentiation-associated gene A; NXP = nuclear matrix protein; RNP = ribonucleoprotein; SAE = small ubiquitin-like modifier; SRP = signal recognition particle; SSA = Sjögren syndrome-related antigen; SUMO = small ubiquitin-like modifier activating enzyme; TIF = transcription intermediary factor; tRNA = transfer ribonucleic acid.

FIGURE 1 Presenting Electrocardiogram



Atrium-sensed, ventricular paced rhythm with heart rate of 129 beats/min.

and steroid myopathy, AMIC best explained these findings given the patient's longstanding exposure to the drug. Her heart failure was recognized only at its end stage and was accompanied by multiorgan dysfunction. This presentation highlights the crucial importance of regular monitoring and early detection of AMIC.

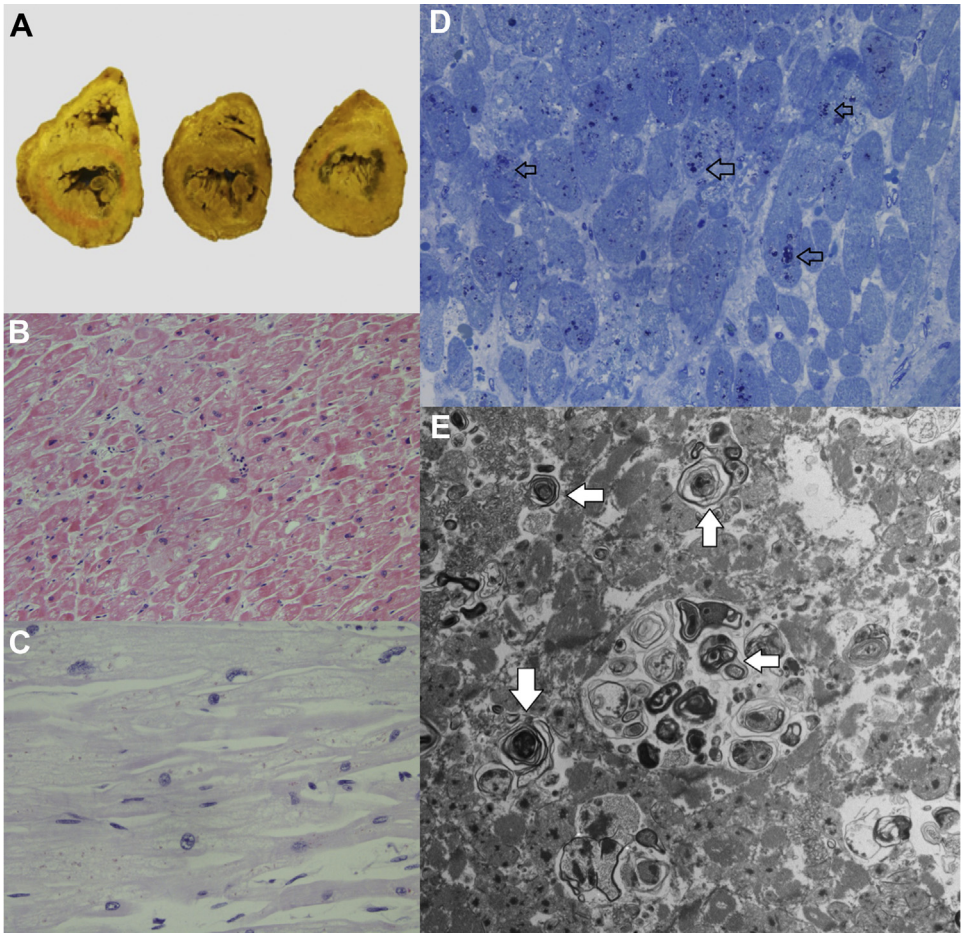
HOW MIGHT CLINICIANS ACROSS SUBSPECIALTIES WORK TOGETHER TO MONITOR FOR CARDIOTOXICITY IN PATIENTS ON ANTIMALARIALS?

Currently, no screening guidelines exist for cardiac monitoring of patients on long-term AM, given limited evidence available to guide specific recommendations. Aside from association with longer duration and higher dosage of medication use, no other risk factors have been recognized (4,9). The true prevalence of AMIC is unknown, but likely underappreciated, given the large number of patients on AM, the lack of recognition of cardiac toxicities, and the variable initial phenotype. Given the high fatality rate, rheumatologists and cardiologists who care for patients on AM must recognize and maintain a high index of suspicion for AMIC.

It is suggested that a baseline electrocardiogram be obtained to assess for conduction abnormalities and history and physical to assess for heart failure should be obtained prior to the initiation of an AM and annually thereafter. Although no routine screening methods such as echocardiography or CMR have been evaluated, BNP concentration is 1 possible way to screen for the development of new heart failure and AM toxicity, within the context of a patient's other comorbidities and individual BNP trend. Syncope, conduction abnormalities, clinical heart failure, or rising BNP level should trigger the echocardiogram and referral to a cardiologist for further evaluation and work up, which may include an EMB and/or CMR. If an EMB is nondiagnostic and the index of suspicion for AMIC remains high, empiric discontinuation of the AM medication should be strongly considered, given the high mortality rate and potential reversal of cardiomyopathy with discontinuation. If the decision is made to continue AM therapy in the setting of a nondiagnostic EMB, CMR can be useful to evaluate for other causes. Staged, repeated EMB can be performed after 1 to 2 months.

When AMIC is suspected or confirmed, a multidisciplinary discussion among rheumatology and cardiology providers and the patient should guide the next steps with shared decision making. If the medication has been effective at suppressing rheumatologic disease and improving quality of life, this must be weighed against the risk of heart failure and mortality, as AM cessation can be lifesaving.

FIGURE 2 Gross and Microscopic Cardiac Pathology



Ventricular cross-sections of the 625-g heart (expected 310 g) showed hyperemic acute subendocardial infarcts of the anterior and posterior left ventricular walls on apical cross-sections **(A)**. Light microscopy examination **(B to D)** showed enlarged myocytes with frequent cytoplasmic vacuolization **(B)** (hematoxylin and eosin stain; 200× original magnification), which are not filled with glycogen **(C)** as shown by negative periodic acid-Schiff stain (400× original magnification). Toluidine blue-stained scout section showed intracellular curled material/cellular debris **(D, arrows)** (200× original magnification). Ultrastructural examination of the myocytes with electron microscopy **(E)** showed intracellular secondary lysosomes and myelin figures **(arrows)** (7,100× original magnification).

ACKNOWLEDGMENTS The authors are grateful to the patient presented in this case report and to her family.

AUTHOR DISCLOSURES

Dr. Lindenfeld has received consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, CVRx, Impulse Dynamics, Edwards Lifesciences, and V-Wave; and grant support from AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS acute heart failure, antimalarial toxicity, cardiomyopathy, chronic heart failure, endomyocardial biopsy, systolic heart failure

APPENDIX For a supplemental video, please see the online version of this paper.