JACC: CASE REPORTS VOL. 2, NO. 3, 2020

MINI-FOCUS ISSUE ON HEART FAILURE

INTERMEDIATE

CASE REPORT: CLINICAL CASE SERIES

Human Monocytic Ehrlichiosis Associated With Myocarditis and Hemophagocytic Lymphohistiocytosis

Cherie N. Dahm, MD, BSN,[a,b] Bin Q. Yang, MD,[c] Daniel E. Clark, MD, MPH,[b] William C. Armstrong, MD,[b] Lynne W. Stevenson, MD[b]

ABSTRACT

We present 3 cases at a single institution of human monocytic ehrlichiosis resulting in myocarditis and hemophagocytic lymphohistiocytosis. Contrary to previously published studies in which case fatalities were only as high as 1%, 2 of the 3 patients we discuss experienced a fulminant course resulting in death despite appropriate doxycycline treatment. Human monocytic ehrlichiosis is rarely a cause of myocarditis and hemophagocytic lymphohistiocytosis, but a high degree of suspicion is important because early empirical therapy may decrease morbidity and mortality. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:420–5) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Human monocytic ehrlichiosis (HME) is a tick-borne illness caused by an *Ehrlichia chaffeensis-, Ehrlichia ewingii-,* and *Ehrlichia muris*-like agent. It typically manifests as a self-limiting, flu-like syndrome, but more severe complications such as meningoencephalitis, respiratory failure, hemophagocytic lymphohistiocytosis (HLH), and (rarely) death can occur. The highest reported occurrence of ehrlichiosis is in the north central United States followed closely by the south central United States (1,2).

Here, we present 3 cases of HME at our institution, all associated with dysregulated immune activation diagnostic of HLH and varying severities of myocarditis and multiorgan dysfunction (3–5).

LEARNING OBJECTIVES

- A high clinical suspicion for tick-borne illness and prompt initiation of doxycycline therapy is necessary in endemic areas.
- HME can be a rare cause of both myocarditis and HLH and when associated with these conditions is often fatal without prompt recognition and treatment.

CASE 1

Z.K., a healthy 41-year-old trail runner, presented with a 6-day history of high fevers, headache, and weakness in the setting of tick exposure. Pertinent admission laboratory findings are documented in **Table 1**. An electrocardiogram (ECG) was notable for anterior and inferior T-wave inversions (**Figure 1A**).

From the [a]Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; [b]Division of Cardiovascular Medicine, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, Tennessee; and the [c]Division of Cardiovascular Medicine, Barnes-Jewish Hospital/Washington University in St. Louis, St. Louis, Missouri. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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, or patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received August 28, 2019; revised manuscript received December 11, 2019, accepted December 28, 2019.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.12.042

Intravenous (IV) doxycycline was immediately started. On hospital day (HD) 2, a transthoracic echocardiogram (TTE) showed normal left ventricular (LV) size and wall thickness, preserved LV systolic function (ejection fraction [EF] >55%), and focal hypokinesis of the mid-lateral wall (Figures 1A and 1B); an ECG revealed anterior and inferior T-wave inversions (Figure 1C). Infectious disease evaluation revealed positive blood *Ehrlichia* polymerase chain reaction (PCR). The patient was discharged on HD 5 to complete a 10-day course of doxycycline. Z.K. refused cardiac magnetic resonance imaging and bone marrow biopsy due to clinical improvement. At the 2-week follow-up, a repeat TTE showed normalization of his previous wall motion, and an ECG showed resolution of his T-wave inversions (Figures 1D to 1F). Z.K. is back to running.

COMMENTARY. Myocarditis should be on the differential diagnosis of any young, healthy patient with antecedent febrile illness and evidence of myocardial ischemia, such as the ECG changes, wall motion abnormalities, and troponin elevation seen in this patient. Life-threatening forms of myocarditis must be aggressively ruled out, such as giant cell myocarditis, autoimmune myocarditis, anomalous coronary arteries, Kawasaki's disease, and drug-induced myocardial injury should also be considered (4,6).

CASE 2

K.S., a 60-year-old woman, was found unresponsive at home in the setting of 3 days of fevers and malaise. At the OSH, K.S. was in septic shock with blood pressure of 76/42 mm Hg and was treated with IV fluids, piperacillin-tazobactam, and levofloxacin. She was transferred to Vanderbilt for a higher level of care. She quickly developed hypoxic respiratory failure requiring intubation. Further history elicited a tick bite 1 week before presentation, for which IV doxycycline was initiated on HD 3. Pertinent admission laboratory findings are documented in Table 1. Peripheral blood smear identified intracellular organisms consistent with HME, corroborated by positive blood *Ehrlichia* PCR. Computed tomography chest imaging revealed multifocal pneumonia. Cerebral spinal fluid (CSF) analysis from lumbar puncture was normal with 1 nucleated cell, glucose 58 mg/dl, and protein 61 mg/dl. CSF was later found to have positive *Ehrlichia* PCR. On HD 2, an ECG showed <1 mm ST-segment elevation in lead V_3 with nonspecific ST-T changes (Figure 2A), then later atrial fibrillation with rapid ventricular response (Figure 2B). The patient's TTE showed normal LV size and wall thickness, severe inferior and inferoseptal wall hypokinesis, and severely depressed LV systolic function (EF 25% to 30%) (Figures 2C to 2F). Due to rising troponin levels, the patient underwent left heart catheterization, which revealed nonobstructive coronary disease (Figures 2G and 2H). Due to multiorgan failure, hematology deferred treatment for secondary HLH. On HD 4, brain magnetic resonance imaging results suggested encephalitis. With the grim prognosis, the family elected transition to comfort care. K.S. died on HD 12 due to cerebral herniation from presumed HME-induced encephalitis. An autopsy was declined.

COMMENTARY. In comparing this case and the earlier case, the rapid progression of illness with delayed treatment highlights the importance of early treatment with doxycycline in patients with acute febrile illness in tick-borne disease-

ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram
EF = ejection fraction
HD = hospital day
HLH = hemophagocytic lymphohistiocytosis
HME = human monocytic ehrlichiosis
IV = intravenous
LV = left ventricular
OSH = outside hospital
PCR = polymerase chain reaction
TTE = transthoracic echocardiogram

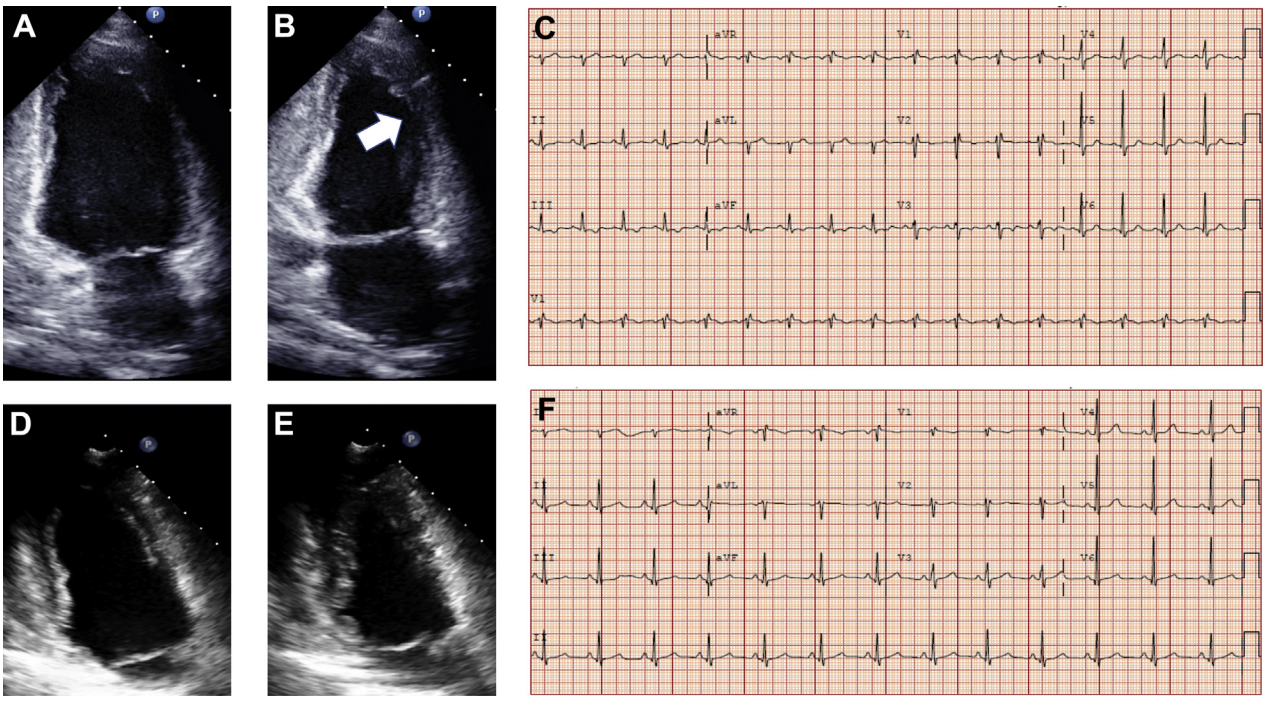
TABLE 1 Laboratory Values

	Case 1		Case 2		Case 3	
	Admission	Day 3	Admission	Day 3	Admission	Day 3
WBC, $\times 10^3$ cells/mm^3	1.5	2.1	3.1	23.2	2.4	9.2
ANC, $\times 10^3$ cells/mm^3	1.2	1.5	2.3	-	0.9	5.8
Hemoglobin, g/dl	11.4	11.3	12.7	9.3	10.7	10.1
Hematocrit, %	33	32	37	27	33	30
Platelets, $\times 10^3$ cells/mm^3	37	55	50	57	48	46
Sodium, mmol/l	128	135	137	141	140	137
BUN, mg/dl	19	10	43	57	80	45
Creatinine, mg/dl	1.37	0.93	2.37	2.63	6.40	3.01
AST, U/l	2,244	995	625	807	582	1,326
ALT, U/l	1,067	667	109	135	130	257
Troponin I, ng/ml	1.02	0.20	0.49	64.40	33.60	21.00
BNP, pg/ml	-	-	104	-	1,047	-
CK, U/l	219	-	4,926	36,004	3,656	25,343
Blood *Ehrlichia* PCR	Positive		Positive		Positive	
Hemophagocytic lymphohistiocytosis criteria						
Fever (>38.5°C)	Yes		Yes		Yes	
Splenomegaly	No		No		No	
Cytopenias*	Yes		No		Yes	
Hemophagocytosis†	-		-		-	
Ferritin, ng/ml	57,356		>40,000		97,053	
Fibrinogen, mg/dl	243		128		121	
Triglycerides, mg/dl	142		843		850	
sIL2,‡ U/ml	4,636		2,178		11,540	
NK cell function§						
E:T ratio (50:1)	5%		3%		9%	
E:T ratio (6:1)	0%		0%		0%	
NK lytic units	0.1		0.0		1.2	

*Presence of cytopenia in 2 of 3 cell lines (absolute neutrophil count [ANC] <1,000; hemoglobin <9; platelets <100,000). †Seen on biopsy of bone marrow, liver, spleen, or lymph node specimen. ‡Reference range, 45 to 1,105 U/ml. §Reference effector:target (E:T) ratio (50:1) >20%, E:T ratio (6:1) >1%, lytic units >2.6.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CK = creatine kinase; NK = natural killer; PCR = polymerase chain reaction; sIL2 = soluble interleukin 2 (alpha subunit); WBC = white blood cells.

FIGURE 1 Echocardiogram and Electrocardiogram Showing Anterior Wall Motion Abnormality With Anteroseptal T-Wave Inversions



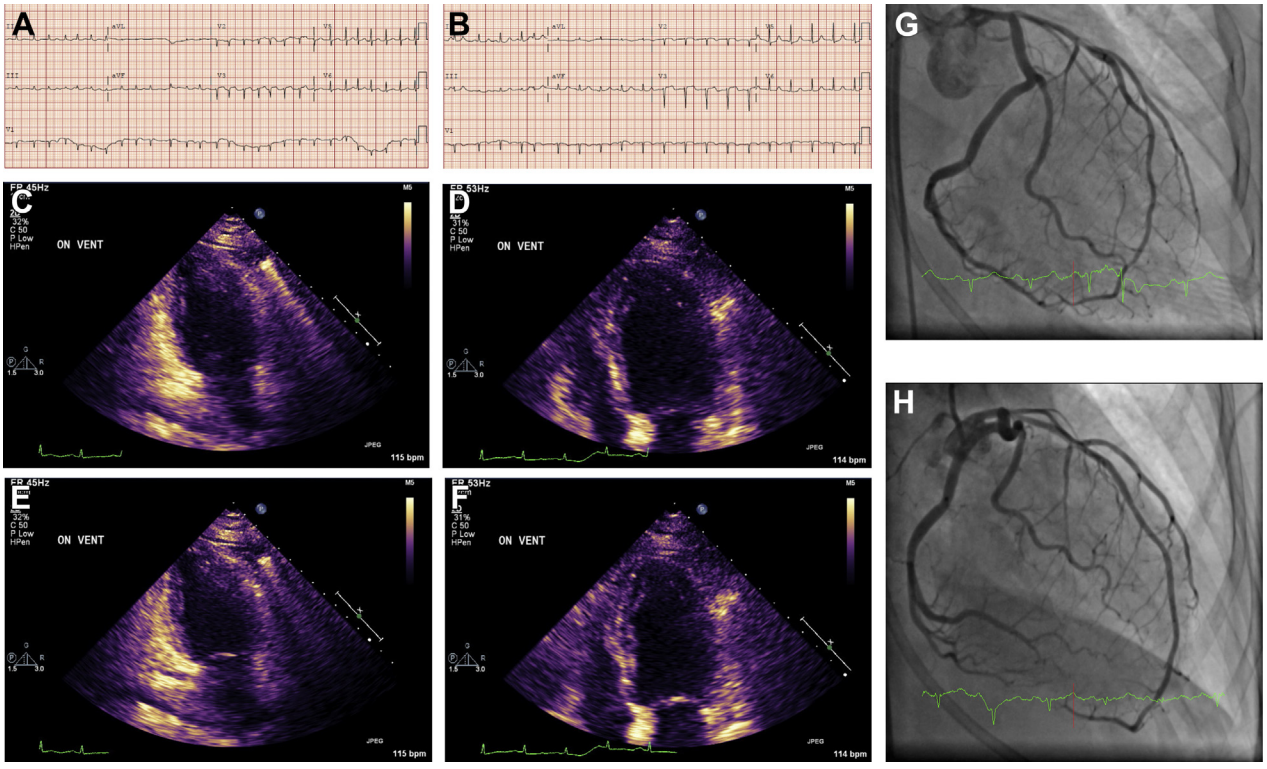
(A) Echocardiogram in 2-chamber view in diastole. **(B)** Echocardiogram in 2-chamber view in systole with notable wall motion abnormality. **(C)** Electrocardiogram with T-wave inversions. **(D)** Echocardiogram 2-chamber view in diastole. **(E)** Echocardiogram 2-chamber view in systole with resolution of wall motion abnormality. **(F)** Electrocardiogram with normalization of T-wave inversions. **A to C** are during acute presentation; **D to F** are from after recovery at follow-up.

endemic areas. There is evidence to suggest that early treatment with doxycycline can reduce morbidity and mortality in patients infected with ehrlichiosis. Typically, defervescence occurs within 24 to 48 h of treatment. Illness severity has been found to directly correlate with longer times between the onset of symptoms and the initiation of treatment (4).

CASE 3

Z.C. is a 68-year-old man who presented to an OSH with a 3-day history of fevers and malaise, empirically treated with vancomycin and cefepime for presumed sepsis. Patient history revealed tick exposure 2 weeks before presentation, and doxycycline was initiated on HD 5. The patient was intubated for hypoxic respiratory failure and started on vasopressors for shock. He was transferred to Vanderbilt for a higher level of care. Pertinent admission laboratory findings are documented in Table 1. On HD 2 at our institution (overall HD 7), TTE showed normal LV size and wall thickness, global hypokinesis, and mildly reduced LV systolic function (EF 40% to 50%) (Figures 3A and 3B). The patient's ECG was notable for new atrial fibrillation with rapid ventricular response, deteriorating to sustained ventricular tachycardia requiring multiple cardioversions (Figures 3C to 3E). TTE showed normal LV size and wall thickness, global hypokinesis, and mildly reduced LV systolic function (EF 40% to 50%). Infectious disease, nephrology, and hematology were consulted. Results of the OSH blood *Ehrlichia* PCR returned positive. The patient was initiated on continuous renal replacement therapy, and dexamethasone was started for secondary HLH. On HD 3, the patient lost brainstem reflexes. A head computed tomography scan showed diffuse white matter edema and midline shift of 10 mm. With the grim prognosis,

FIGURE 2 **Electrocardiogram and Echocardiogram Showing T-Wave Changes and Wall Motion Abnormalities, Respectively, and Coronary Angiogram Showing Nonobstructive Coronary Artery Disease**



(A) Admission electrocardiogram showing sinus tachycardia, <1 mm ST-segment elevation in lead V_3, and T-wave inversions in leads V_1 to V_3. **(B)** Day 3 electrocardiogram showing atrial. Echocardiogram images in **C to F** all show severe inferior and inferoseptal wall hypokinesis and depressed left ventricular ejection fraction (25% to 30%). **(C)** Echocardiogram in 2-chamber view in diastole. **(D)** Echocardiogram in 2-chamber view in systole. **(E)** Echocardiogram in 4-chamber view in diastole. **(F)** Echocardiogram in 4-chamber view in systole. **G and H** show left heart catheterization indicating nonobstructive coronary artery disease. Of note, right coronary artery (RCA) was a small, nondominant vessel with no angiographic evidence of disease (image not shown). **(G)** Left heart catheterization in right anterior oblique caudal. **(H)** Left heart catheterization in in right anterior oblique cranial.

the family elected to transition to comfort care. Z.C. died on HD 3, and an autopsy was declined.

COMMENTARY

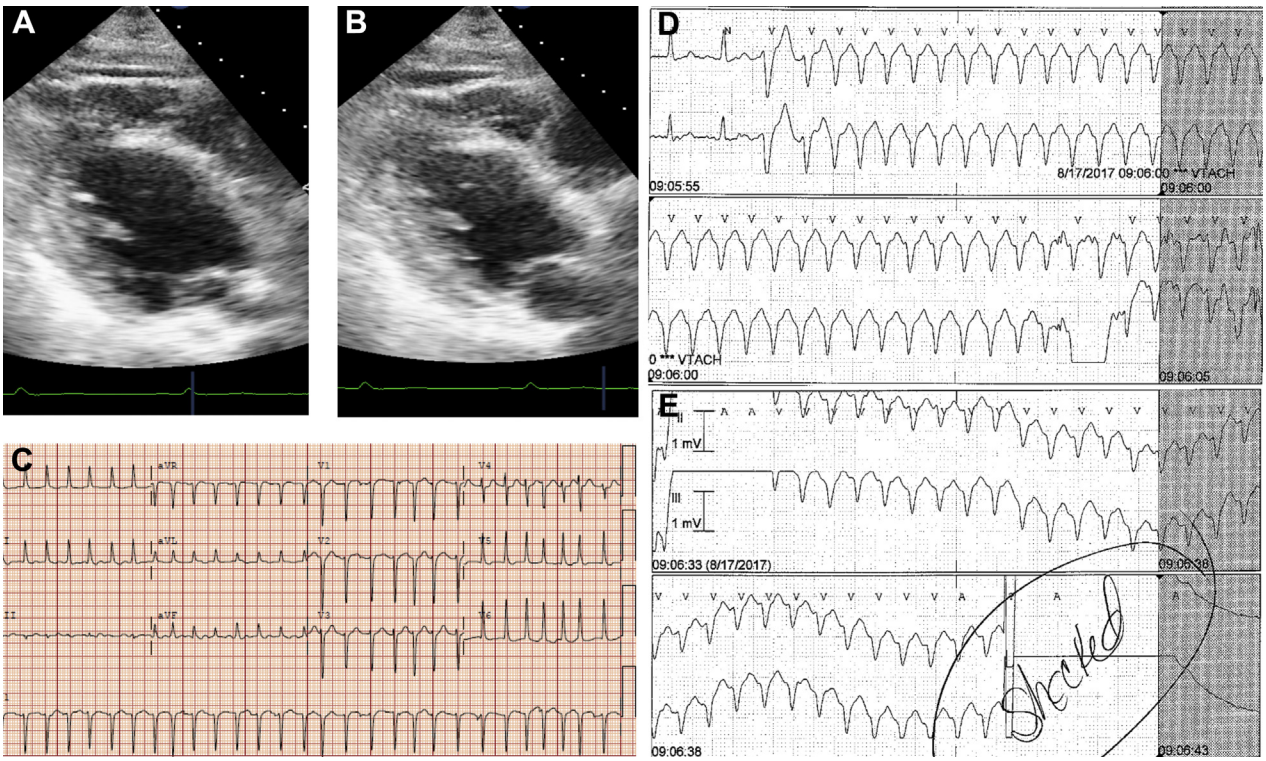
Acute myocardial inflammation from myocarditis is known to be proarrhythmic. Common ECG changes associated with myocarditis are sinus tachycardia and pseudo-infarct patterns with nonspecific ST- or T-wave changes as noted in the 3 cases discussed here. Supraventricular and ventricular arrhythmias are also seen in myocarditis, such as observed in the second and third cases. The second case provides an example of a supraventricular arrhythmia, and the final case describes more malignant ventricular arrhythmias requiring urgent electrical intervention (4,7).

DISCUSSION

There are few published cases that document myocardial involvement by HME, but concurrent findings of both myocarditis and HLH caused by HME have not been reported. To our knowledge, this report is the first of HME as a cause of simultaneous secondary HLH and myocarditis. All 3 patients had PCR confirmation of HME, met diagnostic criteria for HLH, and had evidence suggestive of myocarditis (elevated cardiac biomarkers, characteristic echocardiographic findings, and presence of arrhythmias).

Rarely, HME has been reported to cause myocarditis or secondary HLH. The dysregulated immune T lymphocytic response in myocarditis may be an

FIGURE 3 **Echocardiogram Showing Global Hypokinesis, and Electrocardiogram and Telemetry Strips Showing Atrial and Ventricular Arrhythmias**



Echocardiogram 2-chamber view in diastole **(A)** and in systole **(B)** showing mildly reduced left ventricular ejection fraction (45% to 50%) with global hypokinesis. **(C)** Electrocardiogram on hospital day 2 notable for new atrial fibrillation with rapid ventricular response. **(D)** Telemetry strip on hospital day 2 with new onset of monomorphic ventricular tachycardia. **(E)** Telemetry strip of monomorphic ventricular tachycardia undergoing synchronized cardioversion.

associated phenomenon of end-organ damage from the overactive inflammatory response of T cells and natural killer cells (8). High clinical suspicion for *Ehrlichia* and recognition of immune dysregulation leading to secondary HLH with initiation of early targeted therapies are critical for treatment of these patients. Careful attention to electrolyte management and monitoring for dysrhythmias and hemodynamic compromise is warranted. The role of immunomodulation is not known for this acute infection (7).

Physicians must maintain high clinical suspicion for fulminant HME in patients presenting with fever, hematologic abnormalities, and multiorgan dysfunction during summer months in endemic areas. Empirical treatment with doxycycline should begin early, while awaiting diagnostic test results, and may reduce morbidity and mortality. Notably, myocardial dysfunction can occur, and clinicians should be alert for arrhythmias and hemodynamic compromise (9).

ADDRESS FOR CORRESPONDENCE: Dr. Cherie N. Dahm, Division of Cardiology, Vanderbilt University Medical Center, Suite 383, 2220 Pierce Avenue, Nashville, Tennessee 37232. E-mail: Cherie.n.dahm@vumc.org. Twitter: @CherieDahm.

REFERENCES

1. Folkema AM, Holman RC, Dahlgren FS, Cheek JE, McQuiston JH. Epidemiology of ehrlichiosis and anaplasmosis among American Indians in the United States, 2000-2007. Am J Trop Med Hyg 2012;87:529–37.

2. Dahlgren FS, Heitman KN, Behravesh CB. Undetermined human ehrlichiosis and anaplasmosis in the United States, 2008-2012: a catch-all for passive surveillance. Am J Trop Med Hyg 2016;94:299–301.

3. Otrock ZK, Gonzalez MD, Eby CS. Ehrlichia-induced hemophagocytic lymphohistiocytosis: a case series and review of literature. Blood Cells Mol Dis 2015;55:191–3.

4. Fishbein DB, Dawson JE, Robinson LE. Human ehrlichiosis in the United States, 1985 to 1990. Ann Intern Med 1994;120:736.

5. Havens NS, Kinnear BR, Mato S. Fatal ehrlichial myocarditis in a healthy adolescent: a case report and review of the literature. Clin Infect Dis 2012;54:e113–4.

6. Pinamonti B, Alberti E, Cigalotto A, et al. Echocardiographic findings in myocarditis. Am J Cardiol 1988;62:285–91.

7. Amyn Malik MNJ, Syed Sohail, Sajad Mir. Human granulocytic anaplasmosis affecting the myocardium. J Gen Intern Med 2005;20:C8–10.

8. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–31.

9. Stone JH, Dierberg K, Aram G, Dumler JS. Human monocytic ehrlichiosis. JAMA 2004;292:2263–70.

KEY WORDS cardiomyopathy, echocardiography, electrocardiogram