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ID CASES

Rabies Encephalitis With Myocarditis Mimicking ST-Elevation Myocardial Infarction

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Rabies virus infection remains a significant public health threat particularly in developing countries without effective canine vaccination programs. After symptoms develop, there is no effective treatment and mortality approaches 100%. In countries such as the United States where human rabies remains rare, initial diagnosis is often delayed. In this study, we describe a case of rabies encephalitis presenting with concern for acute ST-elevation myocardial infarction (STEMI) based on electrocardiogram, laboratory, and exam findings and briefly review the known literature on cardiac involvement of rabies virus infection.

Keywords. canine; encephalitis; human rabies; myocarditis.

CASE REPORT

A previously healthy 65-year-old female presented with 3 days of shortness of breath, right arm paresthesias, and anxiety. She had previously presented to 2 other medical facilities where she was treated for musculoskeletal symptoms and panic attacks. Chest x-ray, electrocardiogram (EKG), troponin, and D-dimer at these visits were unremarkable. Upon presentation to our emergency department, her EKG showed ST elevations in leads V1, V2, and aVR with diffuse reciprocal changes (Figure 1). She appeared tachypneic and distressed. Laboratory values were notable for a troponin of 0.8 ng/mL, potassium of 2.8 mg/dL, lactic acid of 8.78 mmol/L, bicarbonate of 14 mmol/L, and anion gap of 22. Due to concern for myocardial infarction, she was taken emergently for cardiac catheterization, which demonstrated clear coronary arteries. After transferring to the intensive care unit postprocedure, she endorsed ongoing dyspnea and dysphagia. She was intermittently confused, and her husband noted this had been ongoing for several days. She was initiated on nonsteroidal anti-inflammatory drugs for a presumed diagnosis of myopericarditis based on peak troponin levels of 7.8 ng/mL and a transthoracic echocardiogram demonstrating normal ejection fraction and trivial pericardial effusion. Over the first 18 hours of admission, she developed rapidly progressive confusion, combativeness, and autonomic instability. She additionally exhibited choking and gasping when given water for pills. This prompted an inquiry about animal exposures, and she reported being bitten on her right hand by a stray dog in India 5 weeks prior. The morning after admission she became unresponsive and was noted to have copious oral secretions during intubation. Head computed tomography showed no abnormalities, and lumbar puncture demonstrated a white blood cell count of 1/μL (differential: 0% red blood cells, 89% lymphocytes, 11% monocytes/macrophages, 0% neutrophils), lactate of 2.6 mmol/L, protein of 27 mg/dL, and glucose of 89 mg/dL.

Because of the concern for rabies, the state health department and the rabies laboratory at the Centers for Disease Control and Prevention were notified, and antemortem testing for rabies was initiated. On hospital day 3, the direct fluorescent antibody from nuchal skin and real-time reverse-transcription polymerase chain reaction on saliva confirmed active infection with canine rabies virus; serum and cerebrospinal fluid (CSF) antibody testing were negative. After discussions with the family, the team pursued aggressive supportive care and initiation of the Milwaukee protocol, including heavy sedation with midazolam and ketamine to oppose dysautonomia and a targeted serum sodium of >145 mEq/L to oppose cerebral salt wasting [1]. As part of the protocol, weaning of sedation began on hospital day 8. Autonomic instability and bradycardia, including Mobitz type II heart block, were observed with increasing frequency. By hospital day 10, she had periods of paradoxical asystole when stimulated. On hospital day 12, there was persistent absence of immune response based on serum and CSF antibody testing. Given the overwhelmingly poor prognosis at this point, her family transitioned her to comfort measures and she died on hospital day 13. Postmortem temporal lobe biopsy demonstrated numerous eosinophilic intracytoplasmic neuronal inclusion bodies, consistent with Negri bodies (Figure 2).

DISCUSSION

The pathophysiology of rabies is characterized by lyssavirus neuronal tropism, with centripetal spread along peripheral nerves starting from the site of inoculation, followed by widespread replication within the central nervous system (CNS),

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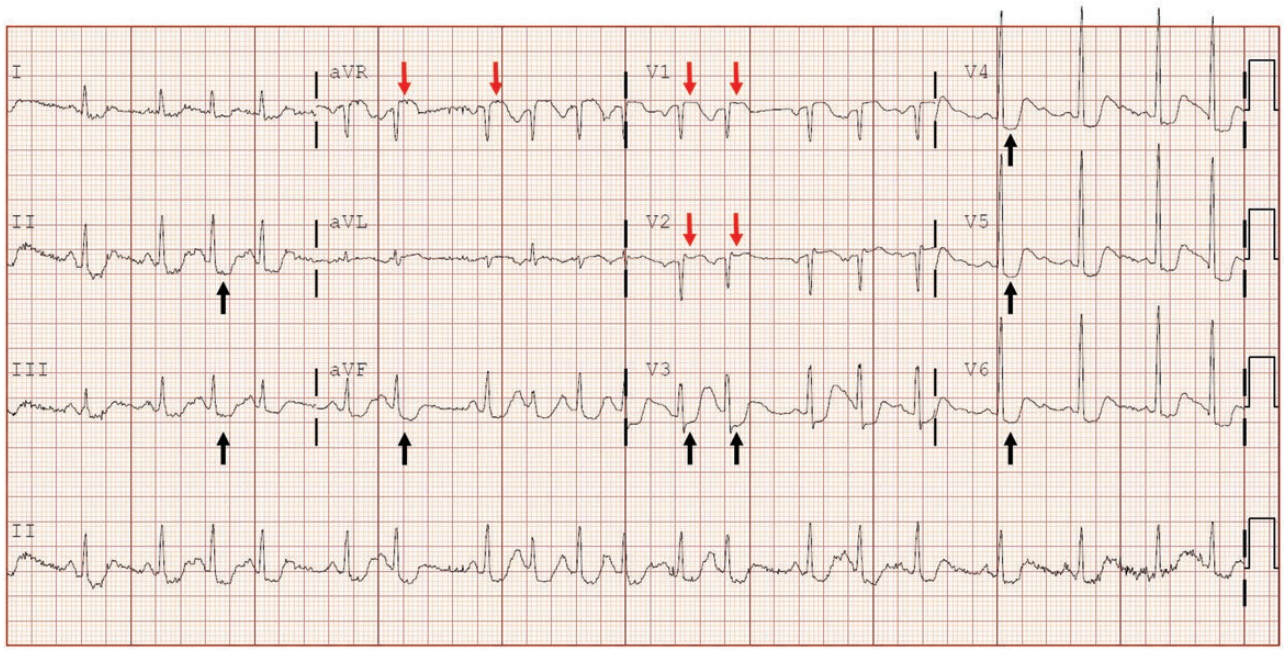

Figure 1. Twelve-lead electrocardiogram showing 1- to 2-mm ST-elevations in leads V1, V2, and aVR (red arrows) and diffuse ST depressions in multiple leads including II, III, aVF, and V3–6 (black arrows).

and finally centrifugal spread to the autonomic nervous system, heart, salivary glands, and adrenal glands [2]. Cardiac involvement in human rabies was first reported in 1962 in a patient who developed nonspecific ST and T wave changes before dying of "refractory cardiovascular collapse" [3]. Dysautonomia and associated arrhythmias, including atrial or ventricular tachycardia and heart block, as in our case, have been previously noted [4–6]. Autopsies show infiltration of cardiac myocytes with neutrophils, lymphocytes, histiocytes, rabies ribonucleoprotein, and Negri bodies localized in cardiac parasympathetic ganglia [3, 5, 7–9]. This patient underwent a limited autopsy that was restricted to the CNS; thus, histologic evidence of cardiac involvement was not obtained. However, her clinical presentation was consistent with myocarditis, and she had no medical history, signs, or symptoms to suggest an alternative etiology. In one postmortem series, 43.5% of human rabies case-patients had evidence of myocarditis [9]. EKG findings that could be mistaken for acute coronary syndrome, such as left bundle branch block, diffuse ST depression, and T wave inversions, have been reported; however, to our knowledge, this is the first report of rabies myocarditis presenting with EKG changes concerning for ST-elevation myocardial infarction (STEMI) [3, 6, 9]. Focal myocarditis has previously been implicated in myocarditis mimicking STEMI; focal inflammatory damage to cardiomyocytes that occurs within a particular arterial distribution creates the same EKG findings as focal damage due to infarction [10–12]. All cases of myocarditis in the previously noted autopsy series were described as "focal interstitial myocarditis" [9].

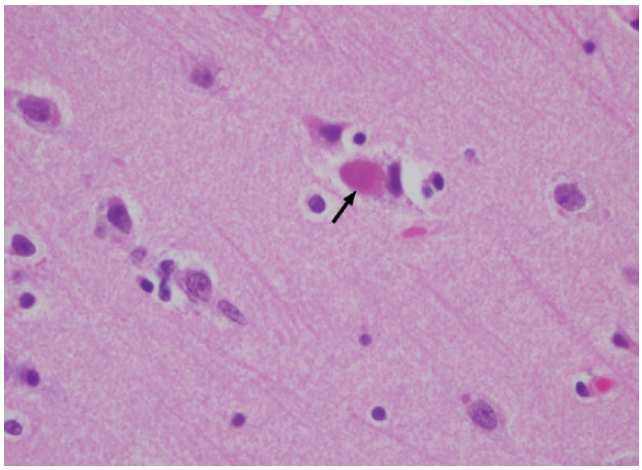

Figure 2. Postmortem hematoxylin and eosin-stained temporal lobe biopsy (×40) showing well circumscribed, eosinophilic inclusion bodies consistent with Negri bodies (black arrow).

CONCLUSIONS

In regions with effective domestic animal immunization programs and in cases where the presenting symptoms are nonspecific, the diagnosis of rabies is easily overlooked. In one series of 32 patients, rabies was included in the differential diagnosis at first hospitalization in only 5 patients [13]. Our patient exhibited intermittent confusion and severe anxiety for several days preceding the development of encephalitis and hydrophobia. This highlights the importance of obtaining a complete social history, including travel and

animal exposures, in patients presenting with new onset neuropsychiatric symptoms. Early diagnosis is critical for the public health response and to allow exposure tracking to consider prophylaxis in other at-risk individuals. Rabies is easily prevented with appropriate pre- and postexposure prophylaxis but is almost universally fatal once symptoms develop [2]. In India, at least 20 000 people die annually from rabies, and 99% of cases are due to exposure to rabid dogs [14]. Patient and public education regarding rabies is critical given the lack of effective therapy once symptomatic. Pretravel evaluations should include a risk assessment for rabies exposure, counseling regarding options for pre- and postexposure prophylaxis, and education about seeking timely medical care if travelers sustain an animal bite.

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References

1. Willoughby RE Jr, Tieves KS, Hoffman GM, et al. Survival after treatment of rabies with induction of coma. N Engl J Med **2005**; 352:2508–14.
2. Singh K, Rupprecht CE, Bleck TP. Rabies (Rhabdoviruses). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia, PA: Elsevier; **2015**.
3. Ross E, Armentrout SA. Myocarditis associated with rabies. Report of a case. N Engl J Med **1962**; 266:1087–9.
4. Cohen SL, Gardner S, Lanyi C, et al. A case of rabies in man: some problems in diagnosis and management. Br Med J **1976**; 1:1041–2.
5. Metze K, Feiden W. Rabies virus ribonucleoprotein in the heart. N Engl J Med **1991**; 324:1814–5.
6. Vassa NT, Yajnik VH, Shah SS, et al. Myocarditis in rabies–clinical and electrocardiographic study of 16 cases. J Assoc Physicians India **1974**; 22:7–11.
7. Cheetham HD, Hart J, Coghill NF, Fox B. Rabies with myocarditis. Two cases in England. Lancet **1970**; 1:921–2.
8. de Morais CF, de Assis RV. Cardiac involvement in human rabies. Case report. Rev Inst Med Trop Sao Paulo **1985**; 27:145–9.
9. Araujo Mde F, de Brito T, Machado CG. Myocarditis in human rabies. Rev Inst Med Trop Sao Paulo **1971**; 13:99–102.
10. Munguti CM, Akidiva S, Wallace J, Farhoud H. ST segment elevation is not always myocardial infarction: a case of focal myopericarditis. Case Rep Cardiol **2017**; 2017:3031792.
11. Nozari Y, Tajdini M, Mehrani M, Ghaderpanah R. Focal myopericarditis as a rare but important differential diagnosis of myocardial infarction; a case series. Emerg (Tehran) **2016**; 4:159–62.
12. Testani JM, Kolansky DM, Litt H, Gerstenfeld EP. Focal myocarditis mimicking acute ST-elevation myocardial infarction: diagnosis using cardiac magnetic resonance imaging. Tex Heart Inst J **2006**; 33:256–9.
13. Noah DL, Drenzek CL, Smith JS, et al. Epidemiology of human rabies in the United States, 1980 to 1996. Ann Intern Med **1998**; 128:922–30.
14. Fitzpatrick MC, Shah HA, Pandey A, et al. One health approach to cost-effective rabies control in India. Proc Natl Acad Sci U S A **2016**; 113:14574–81.