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HEART FAILURE AND CARDIOMYOPATHIES

CLINICAL CASE SERIES

Diphtheritic Myocarditis in an Unvaccinated Child

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ABSTRACT

BACKGROUND Diphtheria, a preventable yet potentially fatal childhood disease, remains a significant threat to unimmunized children, despite its decreased prevalence due to widespread vaccination.

CASE SUMMARY A 6-year-old unvaccinated Spanish boy presented with diphtheritic myocarditis. His condition rapidly deteriorated, leading to cardiogenic shock and ventricular tachycardia, necessitating the use of venoarterial extracorporeal membrane oxygenation and the international procurement of diphtheritic antitoxin (DAT).

DISCUSSION Myocarditis stands as the primary cause of mortality in diphtheria. Early DAT administration is crucial, but its effectiveness diminishes once the diphtheria toxin binds to tissues, and global accessibility may be challenging due to limited production. In scenarios of refractory cardiogenic shock, the employment of mechanical circulatory support, specifically with left cavity drainage systems, can be vital.

TAKE HOME MESSAGES Timely vaccination is crucial in preventing diphtheria-related fatalities. Global access to essential treatments like DAT remains a significant challenge. (JACC Case Rep. 2025;30:102972) © 2025 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/).

A 6-year-old boy was brought to the emergency department with throat pain, difficulty swallowing, and fever. Amoxicillin was prescribed because streptococcal tonsillitis was suspected. Four days later, he was brought back with persistent neck swelling, worse swallowing difficulty, and vomiting. Oropharynx examination revealed a gray-white pseudomembrane with necrotic appearance (**Figure 1**). Because of his family's decision, the child had never received the diphtheria-tetanus-pertussis (DTP3) vaccine.

TAKE-HOME MESSAGES

- Vaccination is essential in preventing diphtheria-related fatalities, underscoring the need for tools to address undervaccination.
- Global accessibility to diphtheria antitoxin is challenging; nonetheless, early administration is essential because its efficacy diminishes when the toxin binds to tissues.

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ABBREVIATIONS AND ACRONYMS

DTP3 = diphtheria-pertussis-tetanus

DT = diphtheria toxin

DTA = diphtheria antitoxin

ECMO = extracorporeal membrane oxygenation

LV = left ventricle

RV = right ventricle

VA-ECMO = venoarterial-extracorporeal membrane oxygenation

WHO = World Health Organization

Under suspicion of diphtheritic tonsillitis, erythromycin was administered, and subsequent throat culture and polymerase chain reaction confirmed the presence of *Corynebacterium diphtheriae*. Samples for Elek's test to assess toxigenicity were sent to a reference laboratory, and the results were considered positive.

After 2 days, worsening symptoms and signs developed, including fluctuations of consciousness, gallop rhythm on auscultation, poor peripheral perfusion, hepatomegaly, and chest petechiae with thrombocytopenia (platelet count 51,000/μL). Blood test results indicated acute renal dysfunction (creatinine 2.61 mg/dL, urea 88 mg/dL), prompting the child's transfer to a tertiary hospital.

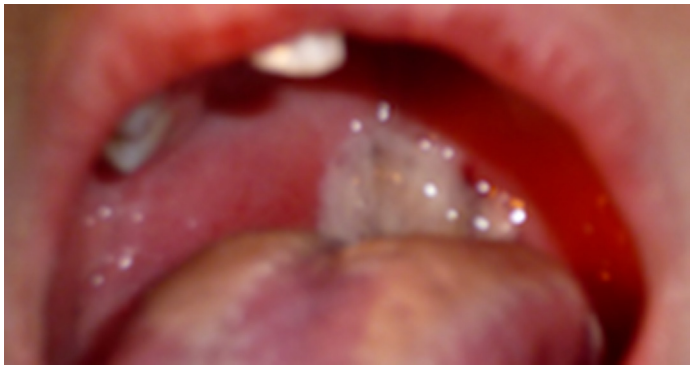
PAST MEDICAL HISTORY

The patient's past medical history was notable only for asthma. As previously stated, he had never received the DTP3 vaccine.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included several serious conditions, given the patient's symptoms and clinical presentation. Sepsis could be considered because of the patient's systemic symptoms and signs, including fever, poor peripheral perfusion, thrombocytopenia, and acute renal dysfunction. These signs indicated a systemic inflammatory response, which could have been caused by a severe bacterial infection spreading beyond the initial site of infection.

FIGURE 1 View of Oropharynx



Gray-white pseudomembrane with a necrotic appearance.

Additionally, bacterial endocarditis was considered because of the presence of systemic and cardiac signs, and the possibility of a secondary infection affecting the heart valves, especially in the context of an ongoing bacterial infection. However, the presence of a gray-white pseudomembrane in the oropharynx strongly suggested a diagnosis of diphtheria, particularly given the patient's lack of DTP3 vaccination.

Finally, while bacterial sepsis and myocarditis were significant considerations, the clinical picture, particularly the pseudomembrane and positive throat culture for *Corynebacterium diphtheriae*, pointed towards diphtheritic myocarditis as the most likely diagnosis.

INVESTIGATIONS

Upon arrival at the tertiary hospital, an acute myocarditis was suspected due to elevated cardiac biomarkers, including troponin I (97 ng/mL), creatine kinase-MB fraction (274 IU/L), and N-terminal pro brain natriuretic peptide (3,103 pg/mL). Echocardiograms revealed severe heart dysfunction (left ventricular ejection fraction 27%) with mild to moderate mitral regurgitation without left ventricle (LV) dilatation (Figure 2) and right ventricle (RV) moderate dysfunction. Chest x-ray revealed pulmonary edema.

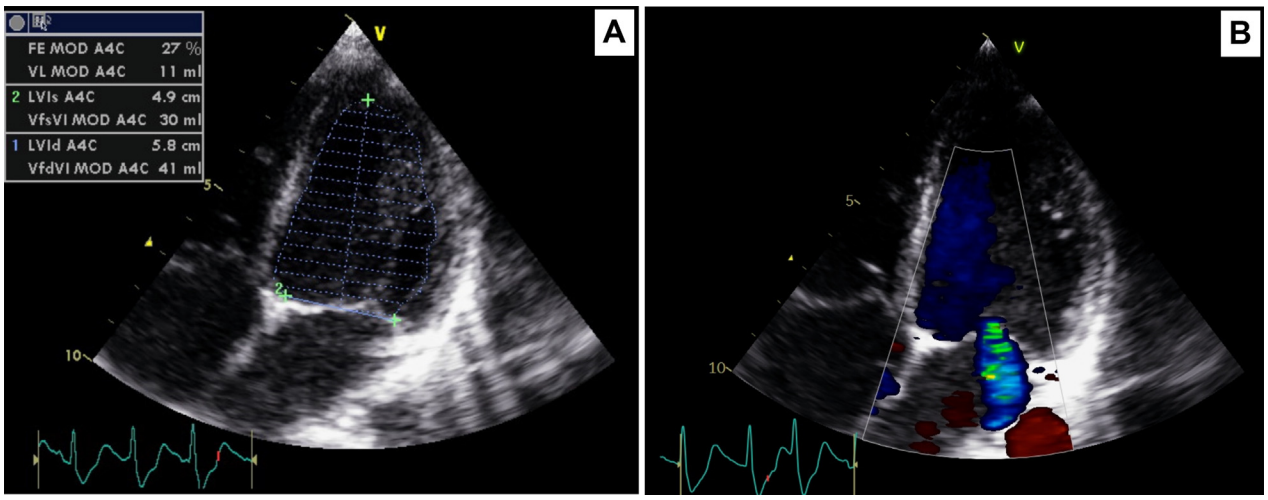
Subsequent electrocardiograms revealed on admission a regularly irregular ventricular tachycardia with alternating tachycardia cycle length, most likely related to the presence of 2 alternative re-entry circuits (Figure 3), which treated with amiodarone changed to an irregular ventricular rhythm from 110 to 143 beats/min with capture beats indicating atrioventricular node integrity.

MANAGEMENT

Because of the patient's hemodynamic instability, he was intubated and given inotropic support, intravenous γ-globulins, antibiotics (penicillin and clindamycin), and carnitine. An international search for diphtheria antitoxin (DAT) was started, and DAT was procured from France and Russia (120,000 IU twice).

Despite medical efforts, the patient's hemodynamic status deteriorated; therefore, venoarterial-extracorporeal membrane oxygenation (VA-ECMO) was initiated, with peripheral cannulation of the neck (right jugular vein and carotid artery). A day later, on the detection of congestion and distention of the left heart, with risk of pulmonary edema, a surgical LV cannula was introduced into the ECMO circuit. Simultaneously, an endomyocardial biopsy was performed, and examination of the biopsy specimen

FIGURE 2 **Echocardiographic Findings**



(A) Heart dysfunction with left ventricular ejection fraction of 27%. (B) Mild to moderate mitral regurgitation.

confirmed inflammatory cardiomyopathy (70 leukocytes/mm^2). Consequently, steroid therapy was started.

OUTCOME

After 22 days of using VA-ECMO, the patient's condition improved (mild dysfunction), and he was successfully weaned from ECMO. However, after he was weaned from ECMO, it become evident that he had experienced cerebral ischemia-reperfusion injury, resulting in brain death, despite medical intervention. A visual summary of the case is shown in **Figure 4**.

DISCUSSION

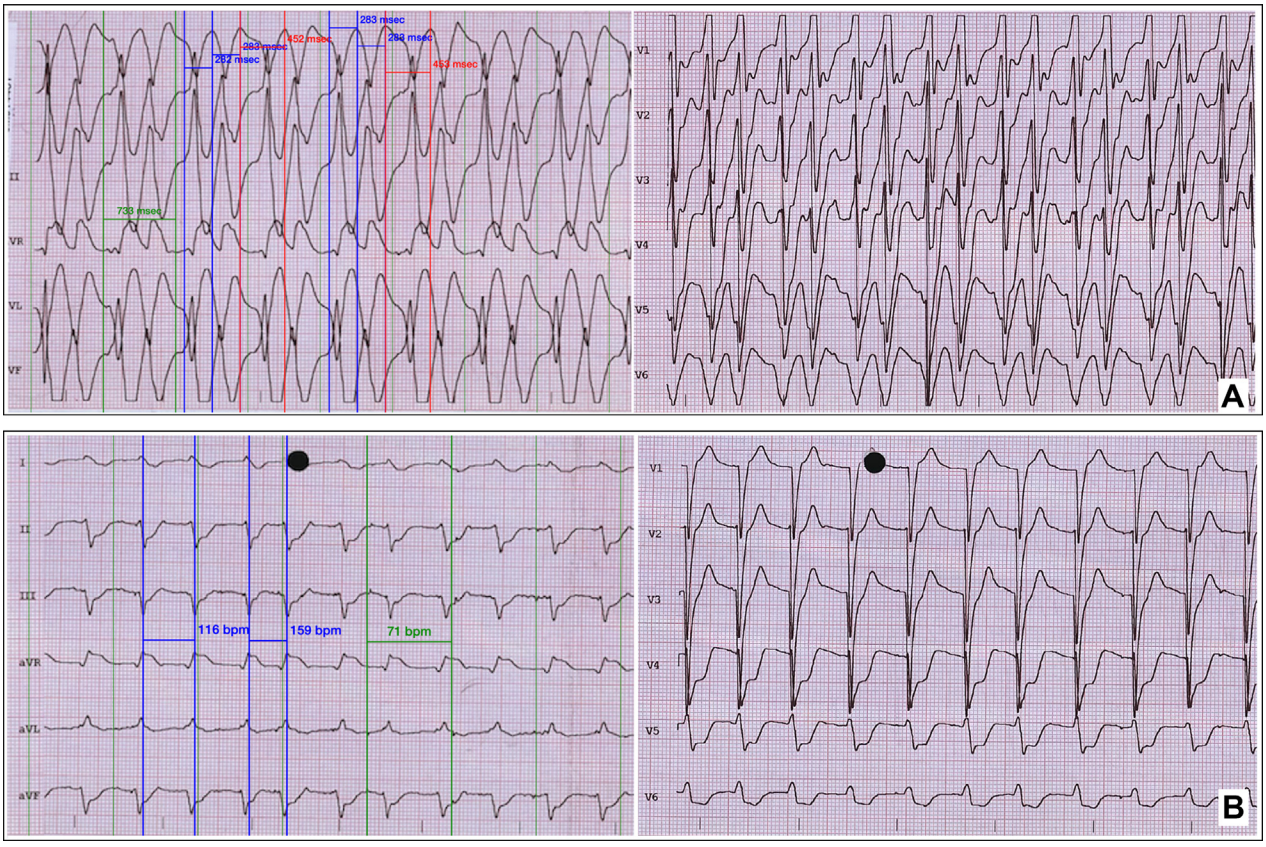
Diphtheria is an infectious disease caused by toxigenic *Corynebacterium*, primarily *C. diphtheriae*. Diphtheria toxin (DT) is the primary virulence factor of *C. diphtheriae*. This exotoxin enters cells via endocytosis as its B-subunit binds to the proheparin-binding epidermal growth factor-like growth factor. Subsequently, DT prevents protein synthesis through its ADP-ribosylation activity, leading to cell death. Disseminatin of DT through the bloodstream from the respiratory tract can result in systemic effects, such as myocarditis.[1,2]

This preventable childhood disease with its high mortality rates represents a significant threat to unimmunized and immunocompromised children.[1,3] In the prevaccine era, it was a major cause of morbidity and mortality, but nowadays, as a result of effective vaccination programs, high-income countries rarely experience cases. However, in low-income countries, diphtheria remains endemic, occasionally leading to outbreaks.[4,5] The rarity of diphtheria in high-income settings may delay the diagnosis until an advanced stage,[3,6] increasing the risk of potentially fatal outcomes.

Vaccination plays an indispensable role in preventing potentially fatal outcomes. Global DTP3 coverage stands at approximately 86% of complete vaccination according to World Health Organization (WHO) estimates.[7] Nevertheless, acceptance or refusal of vaccines is influenced by sociocultural, historical, and political factors and misconceptions regarding vaccine safety and credibility.[1,8] In 2019, the WHO identified the reluctance to receive recommended vaccinations as a top-10 threat to global health, with ongoing efforts to develop tools addressing undervaccination.[9] Effective communication between health care providers and parents about vaccine benefits, risks, and safety increases parental confidence in vaccination decisions.[8]

Myocarditis is the primary cause of mortality in diphtheria (mortality rate of 14%-74%),[1,2] with a wide clinical presetation.[10,11] Most patients show a cardiomyopathy-like presentation, and conduction abnormalities develop in approximately half, contributing to fatal outcomes.[2] An initial clinical improvement can confuse clinicians overlooking the potential fatal late toxin effect.[6] The interval between

FIGURE 3 Electrocardiographic Findings



(A) On admission: regularly irregular ventricular tachycardia with right bundle branch block and superior axis. Interestingly, the tachycardia showed 2 alternating cycle lengths (2 short cycles at 282 ms (blue lines) and 1 longer cycle at 452 ms (red lines) with ventricular-atrial dissociation with an underlying atrial rhythm at 733 ms (green lines). (B) After treatment with intravenous amiodarone: irregular ventricular rhythm with left bundle branch block, superior axis with heart rate between 116 and 143 beats/min (blue lines). Atrial rhythm at 71 beats/min (green lines) with capture beats explain the anticipated ventricular beats indicating atrioventricular node integrity.

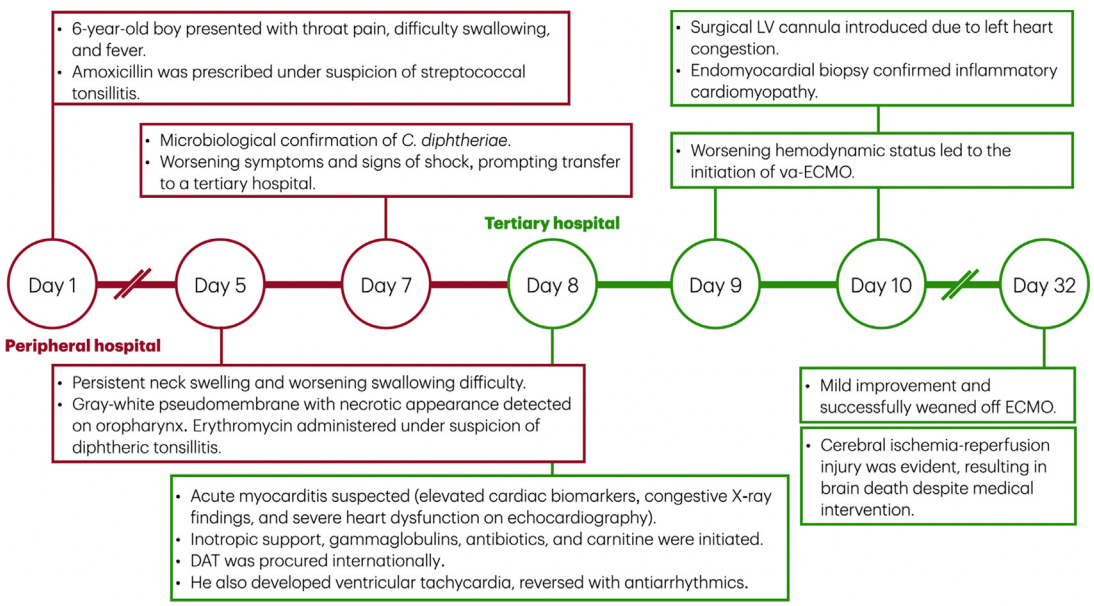
the onset of symptoms and myocarditis is usually 6 to 9 days, being reported ≤25 days;[11] in our case, it was 7 days.

In this context, cardiac enzymes, especially troponin and creatine kinase-MB fraction, serve as reliable indicators of mortality risk,[6] with both parameters markedly elevated in the case here described. Mortality has also been linked to complete heart block or tachyarrhythmias,[11] criteria that our patient also met.

Early administration of DAT is crucial; however, its effectiveness diminishes once DT has adhered to body tissues because DAT is unable to act on the toxin bound to the myocardium.[5,6,11] Therefore, prompt administration after a presumptive diagnosis is essential, as delays are associated with higher mortality.[10,12] Despite being considered an essential medicine by the WHO, global access to DAT is challenging because of limited production and economic incentives, given the low incidence of diphtheria.[1,12] Many countries lack DAT, potentially causing treatment delays.[3,6,12] In our case, DAT was not initially indicated and had to be imported internationally, emphasizing the global availability issue, and myocardial function deteriorated despite antitoxin administration. Whereas research for alternatives, like monoclonal antibodies, is ongoing, none is currently available.[13]

Regarding other treatments, DT induces carnitine depletion, disrupting the oxidation of long-chain free

FIGURE 4 Visual Summary of the Case Report



va-ECMO = venoarterial extracorporeal membrane oxygenation; DAT = diphtheria antitoxin.

fatty acids, and supplementation with carnitine may enhance ventricular function and reduce mortality.[1-14]

In fulminant myocarditis, mechanical circulatory support with ECMO may be necessary. To prevent left heart congestion and pulmonary edema in this case, a surgical LV cannula was inserted. A drainage system is usually required to facilitate ventricular rest and recovery. Nowadays, in our hospital we routinely perform percutaneous atrial septostomy for all patients with severe LV dysfunction requiring VA-ECMO support,[15] a procedure that also allows for endomyocardial biopsy when necessary.

CONCLUSIONS

This rare case highlights the vital role of vaccination in preventing potentially fatal outcomes related to diphtheria. It emphasizes the importance of early DAT administration despite global access challenges. The use of mechanical circulatory support with left cavity drainage systems may be useful in managing fulminant cases. This report contributes to the understanding of the clinical challenges associated with diphtheria.

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KEY WORDS **diphtheria, diphtheria antitoxin, diphtheritic myocarditis, extracorporeal membrane oxygenation, vaccination**