

Unusual Presentation of Dengue Fever

A child with acute myocarditis

Moaz Aslam,¹ Numra A. Aleem,¹ *Mohammad F. Zahid,¹ Arshalooz J. Rahman²

تجلي غير معتاد لحمي الدنك حالة طفل مصاب بالتهاب عضل القلب

معاذ أسلم، نمره عبد العليم، محمد فيزان زاهد، أرشلوز جميلة رحمن

ABSTRACT: Dengue fever (DF) is an acute febrile illness that follows a self-limiting course. However, some patients suffer from complications, including myocarditis, due to the involvement of other organs. A child presented at the Aga Khan University Hospital in Karachi, Pakistan, in June 2013 with a high-grade fever, *malaise* and epigastric pain radiating to the chest. Positive DF antigen and immunoglobulin M assays confirmed the diagnosis of DF. Persistent bradycardia with low blood pressure led to further cardiac investigations which showed a decreased ejection fraction and raised serum cardiac enzymes, indicating myocardial damage. With supportive care and use of inotropes, the spontaneous normalisation of cardiac enzyme levels and ejection fraction was observed. The child was discharged five days after admission. This case highlights the importance of identifying myocarditis in DF patients suffering from cardiac symptoms that are not explained by other potential aetiologies. Awareness, early suspicion and supportive care are essential to ensure favourable outcomes.

Keywords: Dengue Fever; Myocarditis; Complications; Child; Case Report; Pakistan.

المخلص: حمى الدنك علة حمى حادة محددة ذاتيا. غير أن بعض المرضى بها قد يعانون من مضاعفات تصيب أعضاء أخرى مثل التهاب عضلة القلب. تم تسجيل حالة طفل في مستشفى أغا خان في باكستان في يونيو 2013م مصاب بحمى مرتفعة وتوعك وفطور وألم فوق المعدة يمتد للصدر. وأكدت النتائج الإيجابية لمستضد حمى الدنك والغلوبيولين المناعي M تشخيص حمى الدنك. بطء القلب المزمن مع انخفاض ضغط الدم استدعت لمزيد من التحاليل، ووجد أن هناك نقص في الكسر القذفي وارتفاع نشاط انزيمات القلب، مما يدل على ضرر بعض عضل القلب. وتم عن طريق العلاج الداعم واستخدام الأدوية المقوية للتقلص العضلي إعادة نشاط انزيمات القلب والكسر القذفي إلى المعدل الطبيعي. وتم تخريج المريض من المستشفى بعد خمسة أيام بعد دخوله إليها. وتشير هذه الحالة لأهمية التعرف على التهاب العضل عند المصابين بحمى الدنك الذين يعانون من أعراض قلبية لا يمكن تفسيرها أو عزوها لأسباب محتملة أخرى. ويعتمد الحصول على أفضل النتائج على الوعي، والشك الباكر والعلاج الداعم.

مفتاح الكلمات: حمى الدنك؛ التهاب عضل القلب؛ المضاعفات؛ طفل؛ تسجيل حالة؛ الباكستان.

DENGUE FEVER (DF) IS A POTENTIALLY LIFE-threatening vector-borne tropical disease caused by a single-stranded positive-sense ribonucleic acid virus belonging to the *Flaviviridae* family. Outbreaks have increased in severity over the past few years, especially in developing countries in South Asia.^{1,2} The World Health Organization (WHO) estimates that approximately 2.5 billion individuals are susceptible to DF and a 100 million are infected every year.³ While DF is a self-limiting illness in the majority of patients, about 0.5% of patients develop a complicated course requiring specialised therapy.³ A total of 20,000 deaths are reported annually worldwide due to complications associated with severe DF.³ According to the WHO Eastern Mediterranean Regional Office, there have been 16,580 confirmed cases of DF and 257 deaths due to the disease in Pakistan alone since 2010.⁴ There have been several preventable

DF deaths in Pakistan, such as those in the dengue outbreak of 2011.⁵ As such, optimal management and treatment of DF and dengue shock syndrome presents a challenge for healthcare professionals.

Involvement of the cardiovascular system (CVS) with decreased cardiac indices and performance has been observed among patients with this disease.⁶ In addition, other cardiac abnormalities, such as supraventricular tachycardia and atrioventricular conduction defects, have also been noted.¹ Although isolated myocarditis has previously been reported in association with the disease, it is still rare.⁶ This case report presents a child with worsening DF signs and symptoms associated with myocarditis. Management with fluid therapy and inotropic support resulted in a favourable outcome. The patient eventually had a spontaneous recovery and normalisation of ejection fraction (EF) and cardiac parameters.

¹Medical College and ²Department of Pediatrics & Child Health, Aga Khan University, Karachi, Pakistan

*Corresponding Author e-mail: faizanzahid91@hotmail.com

Case Report

A 12-year-old girl presented to the Emergency Department of the Aga Khan University Hospital, Karachi, Pakistan, in June 2013 with a five-day history of high-grade fever associated with lethargy, fatigue, *malaise* and vomiting. She also complained of palpitations and persistent epigastric pain radiating to the chest. Her past medical history was unremarkable, revealing a developmentally normal child with up-to-date immunisations and no history of significant medical illnesses, hospitalisation or congenital abnormalities.

On general physical examination, the child was irritable and had a temperature of 38.9 °C. She was tachypnoeic with a respiratory rate of 30 breaths per minute; otherwise, the remainder of her respiratory examination was normal. A cardiovascular and precordium assessment revealed no audible murmurs or other cardiac abnormalities. Bradycardia (minimum of 50 beats per minute [bpm]) accompanied by intermittent tachycardia (maximum of 112 bpm) and low blood pressure (90/65 mmHg) were noted. The heart monitor showed a sinus rhythm during both bradycardia and tachycardia. The patient did not have a rash and her systemic examination was unremarkable. A complete blood count showed leukopenia (white cell count: $3.2 \times 10^9/L$) and thrombocytopenia (platelet count: $106 \times 10^9/L$). The patient's electrolytes were within normal limits; however, her erythrocyte sedimentation rate was raised (42 mm/hour).

The patient was admitted to the inpatient ward and prescribed intravenous fluid replacement with paracetamol to relieve the fever. Empiric intravenous ceftriaxone was started for a possible enteric fever. Further work-up revealed normal serum amylase levels (52 U/L), making pancreatitis unlikely. A typhidot test and peripheral smear for malarial parasites were both negative. Liver function tests showed elevated alanine aminotransferase and aspartate aminotransferase levels of 49 U/L and 153 U/L, respectively. The patient's symptoms and a reverse ratio of liver function tests suggested a viral fever as a likely possibility. The Platelia Dengue NS1 Antigen (Bio-Rad Laboratories Inc., California, USA) and immunoglobulin M (IgM) assays came back positive, which established the diagnosis of DF. Ceftriaxone was discontinued and serial platelet counts continued to show a persistent decline with a minimum count of $25 \times 10^9/L$ during the following 48 hours.

Subsequently, the patient defervesced and her lethargy improved; however, her bradycardia continued (range: 45–50 bpm) with low blood pressure (95/65 mmHg). Prolonged causes of bradycardia and hypotension were explored with a

12-lead electrocardiography with postural changes. The findings demonstrated a prolonged R-R interval with no changes in the P-R and Q-T intervals, S-T segment or Q-R-S abnormalities, indicating sinus bradycardia. A bedside echocardiogram showed global hypokinesia and a decreased EF of 52%. There was no evidence of pericarditis or pericardial effusion. A creatine phosphokinase-MB test was elevated (455 IU/L). A clinical diagnosis of myocarditis, most likely due to the dengue virus, was made. Although a myocardial biopsy was advised to establish the diagnosis, the procedure was not performed due to the financial constraints of the patient's family.

The patient was prescribed inotropic support with dopamine to improve her cardiac output and maintain normal blood pressure. Management was focused on the symptomatic treatment of DF with serial monitoring of platelet counts. On the fourth day of hospital admission, the patient's platelet count, heart rate and blood pressure had stabilised at $56 \times 10^9/L$, 55–65 bpm and 115/78 mmHg, respectively. A limited follow-up echocardiographic assessment was performed which showed EF normalisation at 62%. She was kept under observation for the following 24 hours. The patient was discharged from the hospital after being prescribed paracetamol and omeprazole with instructions to attend weekly follow-up appointments as an outpatient.

Discussion

Dengue is a non-specific febrile illness, presenting most commonly as either DF or the more severe dengue shock syndrome.^{1,7} Heart involvement and cardiac abnormalities in association with DF have previously been reported in the literature, although they are rare complications.^{1,8–11} The clinical manifestations of heart involvement in DF greatly differ—patients can be completely asymptomatic, have very mild symptomatology or can suffer from severe myocardial damage leading to ventricular failure, global hypokinesia and cardiogenic shock.^{3,12–15} The incidence of cardiac involvement greatly varies. Following the dengue outbreak of 1996 in India, Agarwal *et al.* reported that only one of 206 patients infected with DF showed evidence of cardiac involvement upon CVS examination.¹⁶ In a more recent outbreak of DF in India, 9% of patients showed evidence of myocarditis during the course of their illness.¹⁷ During a DF outbreak in southern Taiwan in 2006, only one of 107 patients with DF had a course complicated by acute myocarditis.¹ Similarly, Kabra *et al.* reported cardiac involvement in 16.7% of 54 paediatric DF patients.⁹ In contrast, other studies have

shown a staggering incidence of cardiac involvement in cases of dengue. Wali *et al.* reported the incidence of cardiac involvement to be 70% in a series of 17 patients.¹¹ In addition, following the dengue outbreak of Sri Lanka in 2005, cardiac dysfunction was reported to be the dominant abnormality (80%) among patients.⁶

This disparity in the proportion of cardiac abnormalities likely arises due to the fact that DF is a spectrum disease which can present with atypical manifestations, haemorrhagic fever or shock syndrome. While tachycardia and a transient decline in cardiac function may vary in intensity, they are present across the spectrum.¹⁸ It is important to differentiate tachycardia due to myocardial involvement; reported incidences of 70–80% may be overestimations.^{6,11} The majority of the patients in the aforementioned studies exhibited diminished cardiac performance, hypotension and reduced EF; however, some did show electrocardiographical changes.⁶ Several other viruses may give rise to myocarditis.^{3,19,20} Although, the possibility of such viruses was not objectively excluded in the present case, other disease processes responsible for high-grade fever and her initial symptoms—particularly enteric fever and malaria—were ruled out. Hence the temporal relationship with the febrile illness, positive IgM and dengue NS1 antigen tests and the presence of leukopenia with thrombocytopenia confirmed the dengue virus to be the most likely aetiological agent.

Recently, isolated DF cases with cardiac involvement have been reported. Guadalajara-Boo *et al.* reported a 65-year-old woman who developed severe hypotension and circulatory collapse due to dengue myocarditis.¹⁴ She required mechanical ventilation and inotropic support with noradrenaline. Additional therapy with methylprednisolone and ribavirin resulted in the resolution of the cardiac manifestations and a favourable outcome.¹⁴ However, fatal outcomes have also been reported. Miranda *et al.* reported a 37-year-old woman with DF who developed fulminant cardiopulmonary failure.³ Despite treatment with mechanical ventilation, vasoactive drugs and inotropic support with dopamine and noradrenaline, the patient died of cardiogenic shock.³

Immune response to the viral infection and the resulting cascade of inflammatory mediators, such as tumour necrosis factor, chemokines and inflammatory cells, plays a key role in myocardial damage.^{8,21} *In vitro* research indicates that the dengue virus raises intracellular calcium in the myocardium, leading to the opening of mitochondrial membrane pores and activation of the intrinsic apoptotic pathway.²² This may be one of the mechanisms that leads to myocardial injury in DF patients and myocarditis

associated with other viral illnesses.²² Direct damage by the virus may be another mechanism of injury, as is seen in myocarditis caused by other viruses.³ In the present case, based on the unremarkable medical history and up-to-date immunisations, it was concluded that the dengue virus was the most likely cause of the myocarditis. Unfortunately, due to the lack of a biopsy and histopathological examination of the cardiac tissue, the complete characterisation of dengue myocarditis was not possible. Another aspect to be explored is the genetic susceptibility to developing specific symptoms of dengue infections in local populations, due to different leukocyte antigens and single nucleotide polymorphisms.

The effect of myocarditis is not only limited to the mechanical functioning of the heart but may also involve electrical conduction. Cardiac rhythm abnormalities have been observed in cases of dengue myocarditis. These include but are not limited to atrial fibrillation, S-T segment abnormalities, low Q-R-S amplitude, sinus bradycardia, first-degree atrioventricular block, premature atrial contractions and premature ventricular contractions.^{8,23} Such conduction defects, which are asymptomatic and self-limiting in the vast majority of patients, can potentially evolve into fatal cardiac arrhythmias.⁸

Hypotension and decreased cardiac function during the course of DF could be attributable to capillary leakage and intravascular volume depletion, leading to haemodynamic instability in these patients.¹⁸ The latter seemed to be unlikely in the current patient, given the fact that she had persistent hypotension which was non-responsive to fluid resuscitation and required inotropic support with dopamine to maintain adequate blood pressure. In such cases, fluid management may need to be reassessed if haemodynamic stability is not achieved with conservative management and fluid resuscitation to avoid volume overload and prolonged tissue hypoperfusion. Children require very specific volumes for fluid resuscitation/therapy and are prone to volume overload states such as pulmonary oedema or superimposed infections.^{3,11} In such circumstances it is necessary to heighten the index of suspicion by reporting to physicians cases with myocarditis as an underlying cause, allowing them to change their approach rather than pursuing vigorous fluid therapy which might be detrimental to the child.^{3,11} Steroids may arguably act as adjuvants to standard therapy due to their anti-inflammatory properties; nevertheless, their role and efficacy has not been established due to a lack of evidence.⁷ The role of cardiac imaging, especially cardiac magnetic resonance imaging, also needs to be assessed in conjunction with electrocardiographical

findings for an effective evaluation, diagnosis and follow-up of such patients.¹⁹ This is a potential topic of future research so that the management of such rare manifestations can be systematised, providing a viable algorithm to avoid preventable deaths, particularly among children. Cardiac imaging was not performed on the current patient due to financial constraints.

Conclusion

The dengue virus is capable of involving multiple organ systems simultaneously or in isolation. Atypical manifestations, such as myocarditis and cardiac dysrhythmias are usually mild or even asymptomatic but can have serious implications on patient outcomes. This case highlights the necessity of awareness, early suspicion and supportive care in achieving a positive outcome for such patients. The role of cardiac imaging needs to be assessed in conjunction with electrocardiographical findings for a clearer evaluation of such cases.

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