



Expanded dengue syndrome in diabetic patient with history of COVID-19 infection: a case report

Erni J. Nelwan, MD, PhD^{a,b,c,d,*}, Pramanta Pramanta, MD^c, Wanda J. Safitri, MD^d, Randy Adiwinata, MD^e, Amy So, MD^c, Leonard Nainggolan, MD, PhD^{a,b}

Introduction: Overlapping symptoms between dengue and coronavirus disease 2019 (COVID-19) may become a diagnostic challenge; moreover, social stigma and fear of being diagnosed with COVID-19 may lead the patients to delayed medical visit. Delayed medical management of dengue may lead to expanded dengue syndrome and a fatal outcome.

Case presentation: A 35-year-old female patient with uncontrolled diabetes mellitus and a recent COVID-19 infection presented with a continuous fever for 4 days. She delayed seeking medical advice due to traumatized being infected by COVID-19, the self-isolation protocol, and the COVID-19 protocol in every hospital for every febrile patient. She developed multiorgan failure during her hospitalization and was diagnosed with expanded dengue syndrome.

Clinical discussion: Diagnosing the etiology of acute febrile illness in the COVID-19 pandemic era is problematic. Most of healthcare facilities warranted COVID-19 evaluation in every acute febrile patient. This protocol may lead to a potential delayed diagnosis and serve as a barrier to accessing healthcare facility. False perception, fear and anxiety of being isolated, discrimination in society, and others may lead to stigmatization of COVID-19 and affect the individual decision for COVID-19 testing and seeking medical advices. Our patient had a fatal outcome due to delayed detection and treatment of dengue hemorrhagic fever.

Conclusion: Delayed management of expanded dengue syndrome leads to a fatal outcome. Stigma may play a role as the barrier for seeking medical advice. Having a broad differential diagnosis in COVID-19 pandemic era is essential.

Keywords: acute febrile illness, case report, coronavirus disease 2019, expanded dengue syndrome, social stigma

Introduction

Dengue infection has been a major health problem, especially in Southeast Asia. Dengue has various symptoms starting from asymptomatic to serious manifestations such as dengue shock syndrome. Prompt diagnosis and appropriate fluid therapy should not be delayed to improve the outcome^[1,2]. Recently, coronavirus disease 2019 (COVID-19) has become a global pandemic worldwide. COVID-19 manifestation varies from mild to severe^[3]. Overlapping symptoms between dengue and COVID-19 may become a diagnostic challenge. Therefore,

^aDepartment of Internal Medicine, Division of Tropical and Infectious Disease, Dr Cipto Mangunkusumo Hospital, ^bFaculty of Medicine Universitas Indonesia, ^cAbdi Waluyo Hospital, ^dMetropolitan Medical Centre, Jakarta and ^eDepartment of Internal Medicine, Faculty of Medicine Sam Ratulangi University, Manado, Indonesia

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Internal Medicine, Division of Tropical and Infectious Disease, Dr Cipto Mangunkusumo Hospital, Jakarta, Postal code: 10430, Indonesia. Tel.: +621 150 0135, fax: +6221 314 8991. E-mail: erni.juwita@ui.ac.id (E.J. Nelwan).

Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Annals of Medicine & Surgery (2023) 85:5187–5190

Received 24 June 2023; Accepted 8 August 2023

Published online 14 August 2023

<http://dx.doi.org/10.1097/MS9.0000000000001201>

HIGHLIGHTS

- Overlapping symptoms between dengue and coronavirus disease 2019 (COVID-19) may become a diagnostic challenge.
- High awareness and a broad differential diagnosis are needed when managing patients with fever presentation in the COVID-19 pandemic era.
- Stigma regarding COVID-19 is playing a significant role as a barrier to accessing healthcare facility.
- Delayed management of dengue hemorrhagic fever leads to a fatal outcome.

having a broad differential diagnosis of fever during the COVID-19 pandemic era is important. The possibility of coinfection should also be considered^[4]. Social stigma and fear of being diagnosed with COVID-19 may lead the patients to delay seeing healthcare professionals^[5]. We present a case of a post-COVID-19 infection patient who failed to be hospitalized timely and leading to expanded dengue syndrome. This case report is reported according to Surgical CAse REport (SCARE) guideline^[6].

Case presentation

A 35-year-old female patient with uncontrolled diabetes mellitus and a history of COVID-19 infection 2 weeks ago presented with a continuous fever for 4 days. The highest recorded temperature was 38.7°C. She also complained of myalgia, headache, and lethargy. She denied any spontaneous bleeding and skin rashes.



Figure 1. Hematomas in patient's extremities.

She denied any significant past and family medical history. She admitted that she delayed coming to healthcare facility due to being traumatized by previous COVID-19 infection, self-isolation protocol, and COVID-19 protocol in every hospital for every febrile patient; even though she just recently recovered from COVID-19 infection. At the emergency-room, her blood pressure was 120/80 mmHg, heart rate was 99 bpm, respiratory rate was 18 time/minute, body temperature was 37.0°C, body weight was 70 kg, body height was 156 cm, and BMI was 28.8 kg/m². Blood examination revealed Hb 20.0 g/dl, Ht 54.9%, WBC 8280/μl, platelet 16 600/μl, and creatinine 1.02 mg/dl. Arterial blood gas showed compensated metabolic acidosis. SARS-COV-2 PCR testing was negative. She was diagnosed as a case of dengue hemorrhagic fever (DHF). She was given crystalloid fluid per WHO fluid therapy protocol. On the second day, she had hematoma on her arms (Fig. 1) and groin area, accompanied by melena. She denied bleeding on other sites. She was reported to have decreased in consciousness on the third day of admission. Repeated complete blood count showed Hb 6.2 g/dl, Ht 16.5%, WBC 8860/μl, and platelet 38 000/μl. She was then referred to ICU of another hospital for further treatment.

The patient arrived at the second hospital in a somnolent state with a blood pressure 120/70 mmHg, heart rate 112 bpm, respiratory rate 24 rate/minute, temperature 36.5°C, and O₂ saturation 98% with 2 liter-per-minute nasal cannula. Physical examination revealed pale conjunctiva, lungs, and heart examination were unremarkable, abdominal tenderness in all abdominal regions with signs of ascites. There were multiple hematomas on the bilateral cubital area, upper arm, and hands. Blood examination showed Hb 4.4 g/dl, Ht 12%, WBC 12 700/μl, platelet 90 000/μl, CRP 57.0 mg/dl, ALT 1226 U/l, AST 1648 U/l, BUN 81 mg/dl, creatinine 5.2 mg/dl, albumin 1.9 gr/dl, capillary blood sugar 320 mg/dl, and positive dengue IgM/IgG. A chest radiograph at admission showed no infiltrate (Fig. 2).

The brain CT-scan was unremarkable. An abdominal CT-scan revealed diffuse fatty liver and fluid collection in the pelvic area with peritoneal inflammation. She was then diagnosed as dengue expanded syndrome, severe anemia secondary to gastrointestinal bleeding, and type 2 diabetes mellitus. She was then given fluid replacement therapy with crystalloid, insulin therapy, and 3 units of packed red cell transfusion. During 5 days course in the hospital, her condition and symptoms were improving. Laboratory parameter showed Hb 9.7 g/dl, Ht 27%, WBC 9700/μl, platelet 108 000/μl; but her creatinine was worsening to 7.7 mg/dl with

BUN 110 mg/dl. On the sixth day, her creatinine level increased to 8.3 mg/dl and she had a loss of consciousness followed by a hypotension episode, desaturation, and decreased urine output. Physical examination revealed rales in bilateral lung fields. A chest radiograph showed infiltrate on both lungs and bilateral pleural effusion (Fig. 3).

She was then intubated, inotropes were initiated, and hemodialysis was started. Post first session of hemodialysis, her oxygen saturation was getting better and her vital signs became stable with vasopressors. The following day, her condition worsened and did not even show any improvement after the second hemodialysis session. She died due to multiorgan failure on the eighth day of admission.

Discussion

Diagnosing the etiology of acute febrile illness in the COVID-19 pandemic era is problematic. The differential diagnosis of acute febrile illness is broad, while some etiologies warrant prompt specific treatment to prevent a worse prognosis. Bhatt *et al.*^[7] have proposed an algorithm to diagnosis the etiology of acute febrile illness during the COVID-19 pandemic era. However,

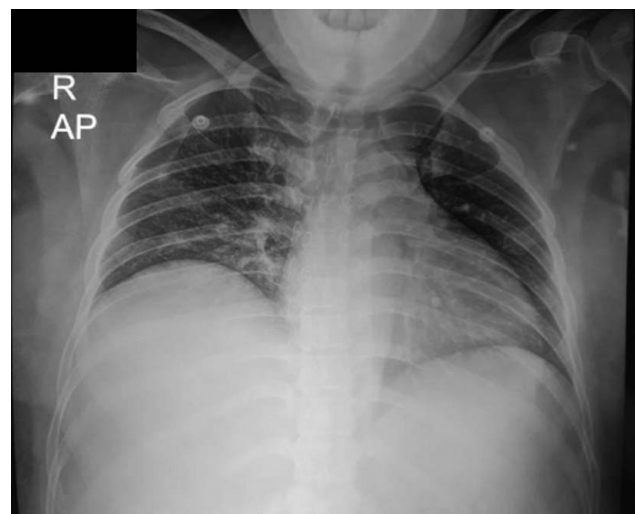


Figure 2. Chest radiograph at admission.

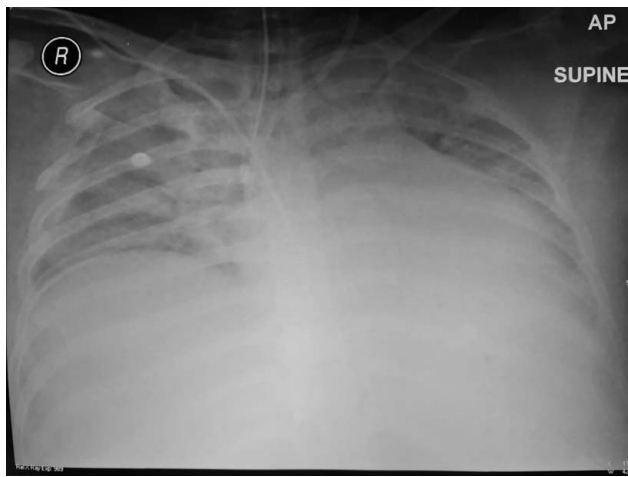


Figure 3. Chest radiograph at the sixth day of hospitalization.

most healthcare facilities warranted COVID-19 evaluation in every acute febrile patient. This protocol may lead to a potential delayed in diagnosis or misdiagnosis for other cause of acute febrile^[5,7]. In our case, the patient was delayed in visiting a healthcare facility after having a febrile episode for four days. She had recently recovered from COVID-19 2 weeks ago and yet she underwent the COVID-19 protocol again in this febrile episode. She was also afraid of being diagnosed again with COVID-19 and needed to be put on self-isolation. The delayed presentation of the DHF led her to an expanded dengue syndrome with a fatal outcome.

DHF is an endemic infection in Southeast-Asia. Early symptoms of dengue infection are unspecific and can be similar with other viral infections such as a mild COVID-19 infection. Alla *et al.*^[8] had listed the comparison between dengue and COVID-19, which share common clinical manifestations that may lead to misdiagnosis.

COVID-19 and dengue had significant difference in management. Delayed management of DHF, especially in the critical phase, may lead to an increased mortality rate^[9]. Therefore, physician should have high awareness and a broad differential diagnosis when managing patients with fever presentation in COVID-19 pandemic era. Ordering specific diagnostic tests, such NS-1, antibody test for dengue, and COVID-19 testing, may help the diagnosis. However, not all healthcare facilities can access those testing, especially in developing countries^[8]. Another challenge is the possibility of coexistent of COVID-19 with other infectious diseases^[5].

Rosso *et al.* found a significant difference between platelet count, neutrophil count, and neutrophil-lymphocyte (NLR) ratio. Therefore, they recommended those laboratory parameters as clue to differentiate COVID-19 and dengue in limited diagnostic access countries^[10]. The use of NLR as a diagnostic and prognostic factor for COVID-19 has been widely researched. Rosso *et al.*^[11] found that COVID-19 patients tend to have lymphopenia, while dengue patients have lymphocytosis. Several mechanisms have been described, such as apoptosis and other, that may lead to lymphopenia occurrence in COVID-19. In our case, we did not have the differential count of WBC at the initial presentation in the previous hospital. Plasma leakage is the hallmark

of DHF, which can be detected by elevated hematocrit from baseline, hypoalbuminemia, ascites, gallbladder edema, and pleural effusion. The critical phase is associated with temporary defervescence^[1]. Our patient presented on the fourth day of fever with elevated hematocrit, a low platelet count, and sign of ascites, suggesting DHF. Increased hepatic transaminases level can be seen in dengue and COVID-19 patients due to their underlying pathophysiology. Rosso *et al.*^[11] found that elevated ALT is more commonly found among dengue patients. Increased hepatic transaminases level is associated with a worse prognosis of dengue and COVID-19 patients^[1,10,11].

Beside the similarity regarding COVID-19 and dengue infection clinical presentations, stigma regarding COVID-19 is playing a significant role as a barrier to access healthcare facility. False perception, fear and anxiety to be isolated, discrimination in the society, and others may lead to the stigmatization of COVID-19 and affect the individual decision for COVID-19 testing and seeking medical advices. Stigma may arise from every role, such as the patients, healthcare professionals, family, employers, and others. Several factors have been described to contribute to COVID-19 stigma, such as insufficient knowledge and awareness, personality, and perceived threats^[12,13]. People who have been fully recovered from previous COVID-19 infections were associated with an increased risk of COVID-19 stigma^[12]. WHO have released guidance to reduce COVID-19 stigma on health workers and families. In that guideline, WHO showed that COVID-19 stigma may manifest as blaming and shaming, indifferent, apathy, exclusion, rejection, denial access, harassment, and victimization. All those behaviors may lead to significant impact on individual, community level, and COVID-19 control. WHO emphasize in sharing COVID-19 fact, mitigating misinformation, enforcing zero tolerance to stigmatization, sharing voices of people whose jobs take care of others, engaging affected communities, reaching out people who suffered from stigma, providing psychosocial support, and promoting social solidarity^[14]. Our patient had history of COVID-19 infection since about 2 weeks prior to admission. Her new onset of fever that started right after she finished her self-isolation discouraged her from having herself checked by the doctor or healthcare facility. That reason contributes to the delay in diagnosing and treatment in this case.

Our patient had a fatal outcome due to delayed detection and treatment of DHF in this patient. She had multiorgan failure. WHO defined expanded dengue syndrome as unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain, heart that associated with dengue infection. Clinician should exclude other cause of the atypical manifestation, beside dengue virus. The mechanisms have not been fully understood, but it was implicated to underlying comorbidities, coinfections, or prolonged shock. Several high-risk groups have been described such as pregnancy, older people, immunocompromised patients^[1,2]. Study also found that diabetes and obesity may serve as possible risk factor for severe dengue. Diabetic patient had dysregulated immune response, dysregulated lipid and phospholipid metabolism, marked endothelial dysfunction and chronic inflammation, due to hyperglycemia, excess free fatty acids, and increased stress oxidative^[15]. Dengue infection may further exacerbate the dysregulated immune condition, endothelial dysfunction, and inflammation in diabetic and obesity patients, leading to more severe disease course. A study in Indonesia showed that patient with nonalcoholic fatty liver disease (NAFLD) was associated with increased hemoglobin concentration, thrombocytopenia, and longer hospital stay.

NAFLD, strongly associated with the metabolic syndrome component, may lead to a more severe dengue course^[16]. Our patient was obese, having uncontrolled diabetes and fatty liver; therefore, she was having high-risk for developing severe dengue or expanded dengue syndrome.

Conclusion

Delayed management of expanded dengue syndrome leads to a fatal outcome. Stigma may play a role as a barrier for seeking medical advice. Having a broad differential diagnosis in COVID-19 pandemic era is essential.

Ethical approval

Universitas Indonesia exempt the need of Ethical Approval for Case report, as it was being reported anonymous and no personal details of the patients being shared.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

None.

Author contribution

E.J.N., P.P., and W.J.S.: involved in patient care, literature review, manuscript writing, editing, and proof reading; R.A., A.S., and L.N.: involved in literature review, manuscript writing, editing, and proof reading. All authors read and approved the final manuscript.

Conflicts of interest disclosures

The authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Erni Juwita Nelwan.

Data availability statement

Available upon reasonable request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgements

None.

References

- [1] Kularatne SA, Dalugama C. Dengue infection: global importance, immunopathology and management. *Clin Med (Lond)* 2022;22:9–13.
- [2] Madanayake P, Jayawardena A, Wijekoon SL, *et al.* Fluid requirement in adult dengue haemorrhagic fever patients during the critical phase of the illness: an observational study. *BMC Infect Dis* 2021;21:286.
- [3] Mesquita RR, Junior LCFS, Santos FMS, *et al.* Clinical manifestations of COVID-19 in the general population: systematic review. *Wien Klin Wochenschr* 2021;133:377–82.
- [4] Tsheten T, Clements ACA, Gray DJ, *et al.* Clinical features and outcomes of COVID-19 and dengue co-infection: a systematic review. *BMC Infect Dis* 2021;21:729.
- [5] Rewerska-Juško M, Rejdak K. Social stigma of patients suffering from COVID-19: challenges for health care system. *Healthcare (Basel)* 2022; 10:292.
- [6] Agha RA, Franchi T, Sohrabi C, *et al.* for the SCARE Group. The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines. *Int J Surg* 2020;84:226–30.
- [7] Bhatt M, Soneja M, Gupta N. Approach to acute febrile illness during the COVID-19 pandemic. *Drug Discov Ther* 2021;14:282–6.
- [8] Alla D, Alla SSM, Vempati R, *et al.* Dengue & COVID-19: a comparison and the challenges at hand. *Cureus* 2022;14:e31877.
- [9] Kalayanarooj S. Clinical manifestations and management of Dengue/DHF/DSS. *Trop Med Health* 2011;39(4 suppl):83–7.
- [10] Rosso F, Rojas OLA. Differentiating dengue from COVID-19: a diagnostic challenge in the tropical regions of the Americas. *Open Forum Infect Dis* 2021;8(suppl 1):S265–6.
- [11] Rosso F, Parra-Lara LG, Agudelo-Rojas OL, *et al.* Differentiating dengue from COVID-19: comparison of cases in Colombia. *Am J Trop Med Hyg* 2021;105:745–50.
- [12] Asadi-Aliabadi M, Tehrani-Banihashemi A, Moradi-Lakeh M. Stigma in COVID-19: a barrier to seek medical care and family support. *Med J Islam Repub Iran* 2020;34:98.
- [13] Duan W, Bu H, Chen Z. COVID-19-related stigma profiles and risk factors among people who are at high risk of contagion. *Soc Sci Med* 2020;266:113425.
- [14] World Health Organization. Regional Office For Africa. Guidance to reduce COVID-19 stigma on health workers and families (Internet). AFRO; 2020. Accessed 31 March 2023. <https://www.afro.who.int/sites/default/files/Covid-19/Technical%20documents/Guidance%20to%20reduce%20COVID-19%20stigma%20on%20Health%20workers%20and%20families.pdf>
- [15] Sekaran SD, Liew ZM, Yam HC, *et al.* The association between diabetes and obesity with dengue infections. *Diabetol Metab Syndr* 2022;14:101.
- [16] Suwanto S, Diahtantri RA, Hidayat MJ, *et al.* Nonalcoholic fatty liver disease is associated with increased hemoconcentration, thrombocytopenia, and longer hospital stay in dengue-infected patients with plasma leakage. *PLoS One* 2018;13:e0205965.