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Secondary dengue serotype 1 infection causing dengue shock syndrome with rhombencephalitis and bleeding associated with refractory thrombocytopenia: A case report

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ABSTRACT

Background: Dengue has a wide spectrum of manifestations, from an asymptomatic condition to dengue shock syndrome. Extensive plasma leakage, severe bleeding, or both, could lead to dengue shock syndrome, a common cause of death in dengue-infected patients. Thrombocytopenia is a common laboratory finding in dengue, which correlates with the disease severity and rapidly resolves during the recovery phase. Therefore, refractory thrombocytopenia is rare in patients with dengue. Rhombencephalitis is an inflammatory disease affecting the hindbrain, rarely associated with dengue. We report the second case of dengue-associated rhombencephalitis, wherein the patient developed dengue shock syndrome and severe bleeding associated with refractory thrombocytopenia.

Case report: A 47-year-old Thai female with secondary dengue serotype 1 infection developed dengue shock syndrome with rhombencephalitis, manifested as altered sensorium and status epilepticus in the critical phase. Cerebrospinal fluid analysis showed pleocytosis with predominantly mononuclear cells and high protein levels. Magnetic resonance imaging of the brain showed multifocal brain signal abnormalities involving the medulla oblongata, pons, midbrain, bilateral hippocampi, thalami, posterior limb of internal capsules, external capsules, and deep hemispheric white matter. The patient had partial neurological recovery following rhombencephalitis for one month. During the recovery phase, severe bleeding with refractory thrombocytopenia and acute kidney injury were observed. Methylprednisolone with eltrombopag was

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administered, which resulted in an increased the platelet count, cessation of bleeding and recovery of kidney function within 4 days.
Conclusions: Dengue is a potential cause of rhombencephalitis. Dengue-associated rhombencephalitis develops during the critical phase, with only partial neurological recovery. However, severe bleeding and refractory thrombocytopenia were also observed during the recovery phase. Methylprednisolone with a thrombopoietin receptor agonist could be an effective treatment for increasing platelet count and stopping bleeding in dengue.

1. Introduction

Dengue shock syndrome (DSS), caused by extensive plasma leakage, severe bleeding, or both, is a common cause of death in dengue-infected patients [1]. According to a recent systematic review and meta-analysis, the magnitude of thrombocytopenia in dengue was 70%, which was higher than the magnitude of prolonged activated partial thromboplastin time in 43% and prolonged prothrombin time in 16% [2]. Previous studies have revealed that thrombocytopenia is associated with dengue severity and a platelet count increases to >50,000/mm^3 from day 8 since fever onset or during the recovery phase [3,4]. Dengue-infected adult patients with thrombocytopenia and poor platelet recovery required longer hospitalisation and had increased risk of bleeding [5].

Encephalitis is a severe and unusual manifestation of dengue [6]. Rhombencephalitis is an inflammatory condition affecting the hindbrain caused by infections, autoimmune diseases, and paraneoplastic syndromes [7]. The common causes of infectious rhombencephalitis are *Listeria monocytogenes*, Enterovirus 71 and *Japanese encephalitis virus* (JEV). Other *Flaviviridae* including *West Nile virus* and *St. Louis encephalitis virus* are rare causes of infectious rhombencephalitis [7]. Dengue-associated rhombencephalitis is also rare, with only one reported case to date [8]. We report the second case of dengue-associated rhombencephalitis, wherein the patient developed DSS and severe bleeding associated with refractory thrombocytopenia. This report follows the CAse REports (CARE) guidelines [9].

2. Case report

A 47-year-old Thai female patient with no significant medical illnesses presented with a two day history of high-grade fever, myalgia, anorexia, nausea, and loose stools. The patient looked fatigued, dehydrated and had a temperature (Temp) of 39.0 °C, pulse rate (PR) of 80 beats/min, blood pressure (BP) of 117/89 mmHg, respiratory rate (RR) of 18 breaths/min, and oxygen saturation (SaO_2) of 98% while breathing room air. Abdominal examination revealed mild tenderness over the right hypochondrium, while the

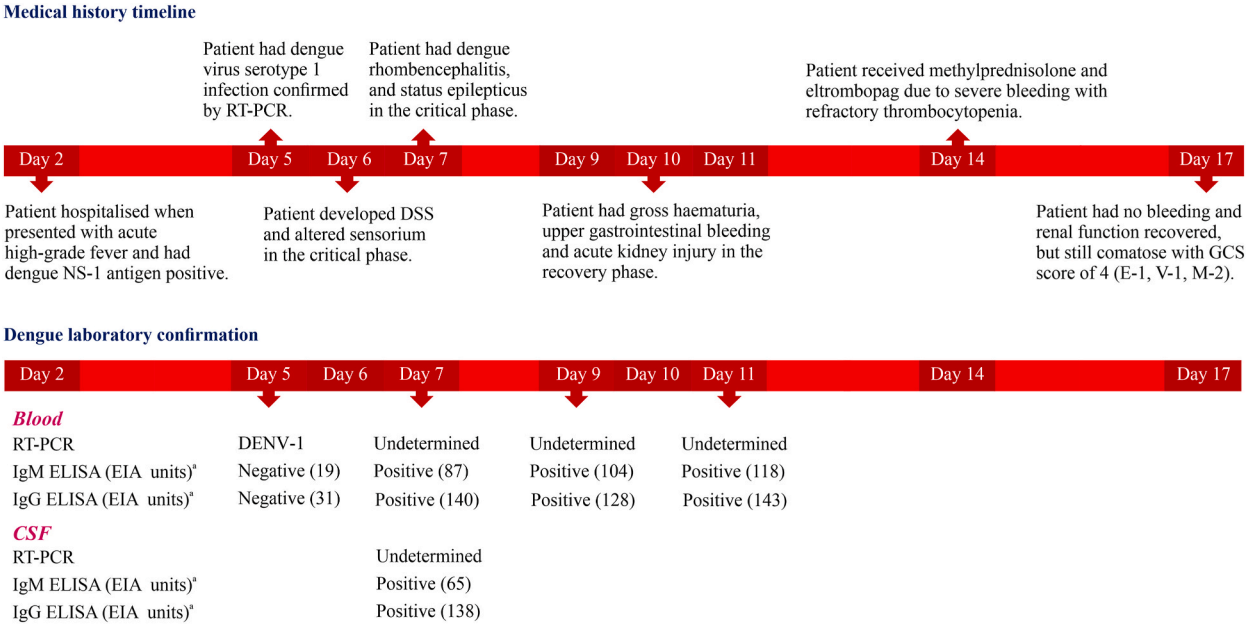

Fig. 1. Medical history and dengue diagnosis timeline of a 47-year-old Thai female patient with dengue shock syndrome, who developed rhombencephalitis and severe bleeding associated with refractory thrombocytopenia by day 2 to 17 since fever onset. Abbreviations: CSF, cerebrospinal fluid; DENV-1, dengue virus serotype 1; DSS, dengue shock syndrome; EIA, enzyme immunosorbent assay; ELISA, enzyme-linked immunosorbent assay; GCS, Glasgow Coma Scale; Ig, immunoglobulin; NS-1, non-structural protein 1; RT-PCR, reverse transcriptase polymerase chain reaction. [a]The EIA ≥40 units is considered positive for IgM antibodies to dengue and the EIA ≥100 units is considered positive for IgG antibodies to dengue.

remaining examination findings were unremarkable. Complete blood count (CBC) showed the following: haemoglobin 13.7 g/dL; haematocrit 38.6%; white blood cell count 6,380 cells/mm^3 with neutrophils 74.1%, monocytes 16.3%, and lymphocytes 9.4%; and platelet count 168,000/mm^3. Blood chemistry showed a random blood sugar of 150 mg/dL, serum creatinine of 0.70 mg/dL, and alanine aminotransferase of 48 U/L. Her urine was deep yellow with a specific gravity of 1.034. Reverse transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2 on nasopharyngeal swab sample was negative while dengue non-structural protein 1 antigen on serum sample was positive. The patient was admitted to Ramkhamhaeng Hospital for fluid replacement therapy with 5% dextrose in normal saline. Fig. 1 depicts the patient's medical history and dengue diagnosis timeline by day 2 to 17 since fever onset. Table S1 shows vital signs, fluid intake/output, laboratory findings, and blood transfusions by day 2 to 19 since fever onset. On day 5 since fever onset, an RT-PCR for dengue on serum sample showed dengue virus serotype 1 (DENV-1).

On day 6 since fever onset, the patient developed DSS with altered sensorium. The fever had subsided and there were no clinical signs of bleeding; however, the patient was disoriented and had cold extremities. Fluid intake was 980 mL in 8 hours, although the urine volume decreased to 200 mL in 8 hours. Vital signs were as follows: BP 106/65 mmHg, PR 70 beats/min (weak pulse), and RR 20 breaths/min with an SaO_2 95% while breathing room air. On auscultation, there were crepitations over both lower lung fields. Chest radiography (CXR) revealed reticular and patchy opacities in both lower lung fields (Table S2). CBC showed: haemoglobin 13.4 g/dL;

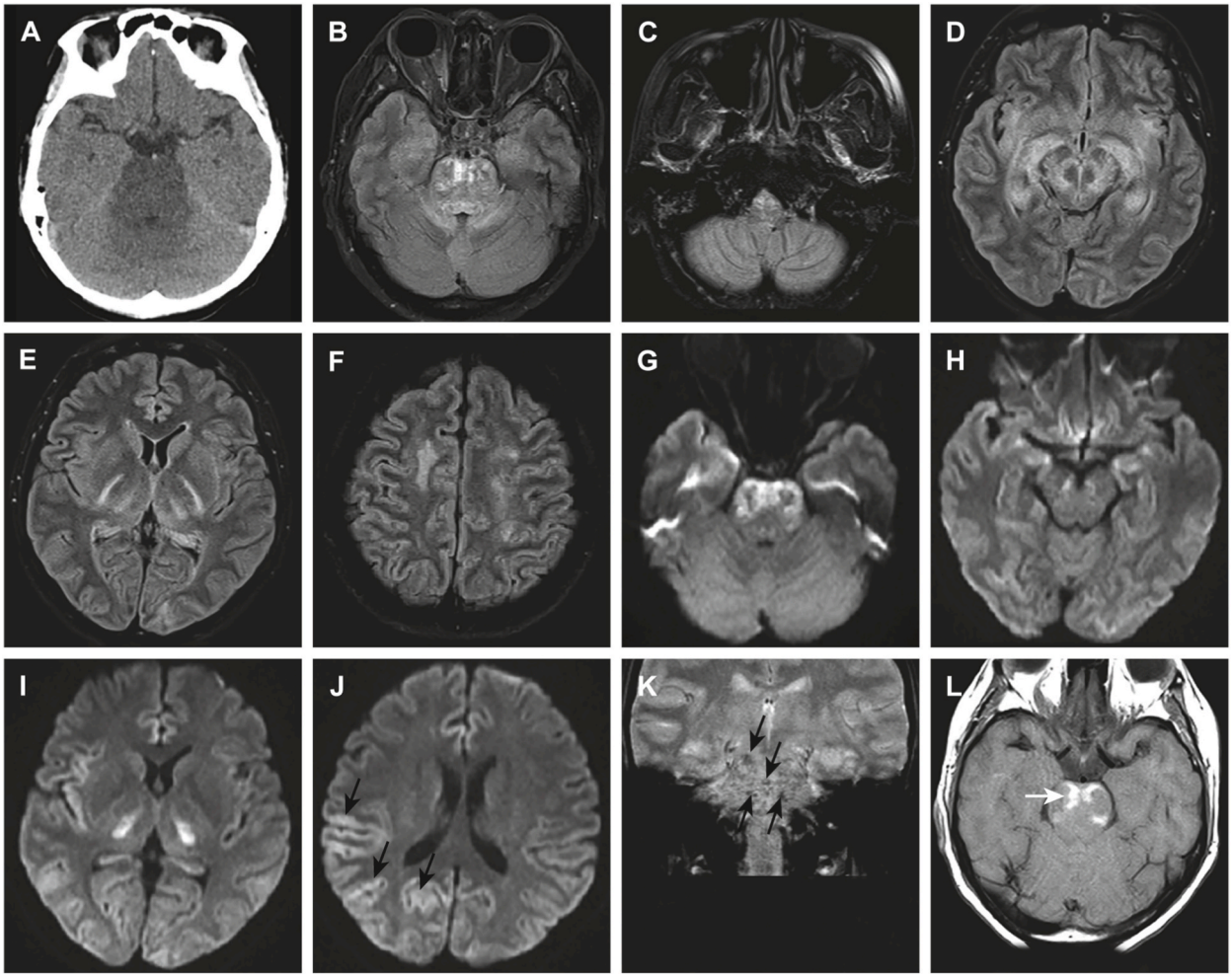

Fig. 2. Non-contrast computed tomography (CT) and magnetic resonance imaging (MRI) of the brain in a 47-year-old Thai female with dengue shock syndrome who developed rhombencephalitis. (A–B) Diffuse oedematous changes in the pons. An axial unenhanced CT image (A) shows abnormal hypoattenuation with swelling of the pons and adjacent cerebellar hemispheres, corresponding to abnormal hyperintensity on T2-weighted fluid-attenuated inversion recovery (T2W FLAIR) MRI (B). (C–J) Multifocal involvement of brain signal abnormalities. Axial T2W FLAIR MRI of four brain regions (C–F) demonstrates the extent of hyperintense signal abnormalities involving the medulla oblongata, pons, midbrain, bilateral hippocampi, thalami, posterior limb of the internal capsules, external capsules, and deep hemispheric white matter. Axial images of four regions of the brain (G–J) obtained using b-1000 diffusion-weighted imaging (DWI) showing restricted diffusion in abnormal areas on FLAIR imaging, with more conspicuous diffusion abnormalities along the cerebral cortex (black arrows). (K–L) Haemorrhage within the oedematous pons. Coronal T2*-weighted gradient echo image (K) shows foci of susceptibility (black arrows) or "blooming artifact" within the pons, which represent foci of haemorrhage. Axial T1W image (L) showing hyperintense signal abnormalities (white arrow) in-keeping with subacute blood products.

haematocrit 39.8%; white blood cell count 4,320 cells/mm^3 with neutrophils 43.0%, lymphocytes 29.0%, and atypical lymphocytes 13.0%; and platelet count 53,000/mm^3. Blood chemistry showed the following: blood sugar 96 mg/dL, serum creatinine 0.70 mg/dL, serum sodium 138 mmol/L, serum calcium 7.6 mg/dL, serum albumin 3.7 g/dL, and alanine aminotransferase 161 U/L. Blood culture showed no growth. The patient was transferred to the intensive care unit, and one unit of leukocyte-poor packed red cells was administered because concealed bleeding was suspected. Pantoprazole 80 mg/day was also administered intravenously. After the transfusion, the pulse was full and extremities were warmer; however, the patient remained disoriented.

On day 7 since fever onset, the patient developed dengue rhombencephalitis with status epilepticus and was drowsy with no response to verbal commands. Vital signs were as follows: Temp 36.0 °C, BP 135/80 mmHg, PR 60 beats/min, RR 34 breaths/min, and SaO_2 99% on an oxygen cannula at 5 L/min. On auscultation, rhonchi were heard over both lungs. Neurological examination showed a Glasgow Coma Scale (GCS) score of 4 (E−1, V−1, M−2), normal reactive pupils of 2-mm diameter, dysconjugate eye movements, decerebrate response, and hyperreflexia. Babinski's sign showed extensor plantar response. CBC showed: haemoglobin 15.9 g/dL, haematocrit 46.7%, and platelet count 44,000/mm^3. Blood chemistry revealed blood sugar 134 mg/dL, blood urea nitrogen 14 mg/dL, serum creatinine 0.51 mg/dL, serum sodium 141 mmol/L, serum calcium 8.2 mg/dL, serum phosphorus 3.3 mg/dL, serum magnesium 1.7 mg/dL, and alanine aminotransferase 176 U/L. CXR showed decreased opacities in both lower lungs (Table S2). Fig. 2A shows the findings of brain computed tomography (CT). Endotracheal intubation was performed, and the patient was placed on ventilator support, following which a generalized tonic-clonic seizure occurred. The seizure was controlled with midazolam, levetiracetam, valproate, and topiramate. Electroencephalography (EEG) showed an epileptiform discharge originating from the left temporal region. Lumbar puncture was performed following the transfusion of two units of leukocyte-poor platelet concentrate. The opening and closing pressures were 30 and 20 cmH_2O, respectively. Cerebrospinal fluid (CSF) analysis showed a white blood cell count of 15 cells/mm^3 with 87% mononuclear cells. The CSF glucose level was 149 mg/dL, with blood sugar 244 mg/dL and CSF protein 871 mg/dL. The RT-PCR results for the CSF viral encephalitis panel test were negative for herpes viruses and other encephalitis viruses (Table S1). RT-PCR for dengue and mycobacterium tuberculosis in CSF were negative. An enzyme-linked immunosorbent assay (ELISA) for dengue-specific antibodies showed positive immunoglobulin (Ig) M (65 EIA units) and IgG (138 EIA units) in the CSF and positive IgM (87 EIA units) and IgG (140 EIA units) in the serum, indicating secondary dengue infection with an IgM/IgG ratio of 0.621. The results of ELISA for IgM and IgG antibodies in the CSF for both JEV and Zika virus (ZIKV) were negative (Table S1). Dexamethasone (16 mg/day) was administered intravenously for 3 days. The medication was then stopped due to no improvement in neurological symptoms and signs, and uncontrolled blood sugar levels despite insulin injections.

On day 10 since fever onset, the patient developed gross haematuria and upper gastrointestinal bleeding with acute kidney injury. Her platelet count was 43,000/mm^3 with normal prothrombin time and activated partial thromboplastin time. In addition, blood urea nitrogen (38 mg/dL) and serum creatinine (1.05 mg/dL) were increased. On days 10 and 11 since fever onset, one leukocyte-poor platelet concentrate unit was administered.

On days 13 and 14 since fever onset, the patient developed severe bleeding with refractory thrombocytopenia and was comatose. Blood analysis revealed decreased haemoglobin (9.5 g/dL), haematocrit (28.1%), and platelet count (34,000/mm^3) and increased blood urea nitrogen (56 mg/dL) and serum creatinine (1.70 mg/dL). CSF culture showed no growth. Direct and indirect Coomb's tests with an antinuclear antibody panel were negative. Immunofluorescence assay for scrub and murine typhus specific IgM and IgG was negative (Table S1). EEG showed no epileptiform discharge. Magnetic resonance imaging (MRI) of the brain and abdominal CT were performed for suspected internal bleeding. Abdominal CT findings were normal (Table S2). Fig. 2B–L shows the findings of the brain MRI. The patient received two leukocyte-poor platelet concentrate units and one leukocyte-poor packed red cells unit along with a single dose of intravenous methylprednisolone (500 mg) and oral eltrombopag (25 mg/day) for 5 days. On day 17 since fever onset, there was no bleeding and the platelet count increased (160,000/mm^3), while serum creatinine (1.30 mg/dL) and alanine aminotransferase (66 U/L) levels decreased.

One month after being diagnosed with dengue rhombencephalitis, a tracheostomy tube was placed and the patient was breathing spontaneously, though exhibiting flaccid quadriplegia. Partial neurological recovery with a GCS score of 9 (E−4, V−1, M−4) was observed. The neurological symptoms and signs did not change during the 6-month follow-up; however, the patient died of aspiration pneumonia in a nursing home.

2. Discussion

In Thailand, the data on encephalitis surveillance and diagnosis between 2013 and 2018 showed that the most common cause of encephalitis was Epstein-Barr virus (27.0%), followed by enterovirus (17.3%), varicella zoster virus (11.3%), human cytomegalovirus (9.7%), herpes simplex virus 1 (7.8%), human herpesvirus 6 (6.3%), *Cryptococcus neoformans/gattii* (5.0%), herpes simplex virus 2 (4.7%), *Streptococcus pneumoniae* (3.5%), *Haemophilus influenzae* (1.9%), *Streptococcus agalactiae* (1.9%), *Escherichia coli* (1.3%), *Neisseria meningitidis* (1.0%), *Listeria monocytogenes* (1.0%), and human parechovirus (0.3%) [10]. Dengue viral encephalitis was observed in only three (0.9%) patients during encephalitis surveillance between 2002 and 2012, with no reported cases of dengue viral encephalitis during encephalitis surveillance between 2013 and 2018 [10].

Verma et al. reported the first case of dengue-associated rhombencephalitis in 2016 [8]. Similar to the present case, the patient had a fever for one week, followed by progressive neurological symptoms and signs involving the brainstem and cerebellum. However, the first case was in good consciousness [8]. The present case of secondary DENV-1 infection developed DSS with rhombencephalitis during the critical phase, manifesting as altered sensorium and status epilepticus. Fever and altered sensorium are common in infectious rhombencephalitis, and only 25% of patients recover completely [7]. CSF analysis showed pleocytosis with high protein levels, indicating an inflammatory process-associated viral invasion [11]. A previous study of brain imaging findings in dengue neurological

infection showed more focal brain lesions on MRI than on CT [12], similar to the present case. The diagnosis of dengue neurological infection in our patient relied on acute signs of central nervous system involvement and positive dengue-specific IgM antibodies in CSF, with exclusion of other causes of encephalitis and metabolic disturbance [13]. In order to exclude infectious causes of encephalitis other than *Flaviviridae*, CSF culture and RT-PCR assay for both encephalitis viruses and mycobacterium tuberculosis were performed. The results were negative. The results of IgM and IgG antibodies by immunofluorescence assay for scrub and murine typhus, a possible cause of encephalitis in tropical countries, were also negative. In Thailand, the common *Flaviviridae* include DENV, JEV, and ZIKV [14]. In the present case, DENV-1 infection was diagnosed by RT-PCR from serum sample on day 5 since fever onset. ELISA testing was also performed on panels of serum samples collected on days 5 to 11 since fever onset to detect antibodies to common *Flaviviridae* in Thailand. The dengue-specific IgM and IgG antibodies were positive on days 7 to 11 since fever onset. The ratio of dengue-specific IgM and IgG antibodies showed secondary dengue infection. The levels of JEV antibodies were higher than the cut-off values on day 9 and day 11 since fever onset for IgM antibodies and on day 11 since fever onset for IgG antibodies. IgG antibodies for ZIKV were also higher than the cut-off values on day 11 since fever onset. However, the levels of IgM and IgG antibodies for JEV and ZIKV were lower than those for DENV. The elevated levels of IgM and IgG antibodies for JEV and ZIKV in the present case might be due to the cross reactivity of antibodies among flaviviruses. On day 7 since fever onset, dengue-specific IgM antibodies by ELISA were positive in the CSF whereas the results of IgM antibodies in the CSF for both JEV and ZIKV were negative. Therefore, dengue neurological infection was diagnosed in the present case. The levels of dengue-specific IgM and IgG antibodies in the CSF were similar to those in the serum, possibly due to increased permeability of the blood-brain barrier. A review of the neuropathogenesis associated with dengue neurological infection suggested that the dengue virus can enter the central nervous system via the bloodstream and infect both neurons and microglial cells, eventually infecting the endothelial cells of the blood-brain barrier. Activated endothelial cells respond to worsening brain inflammation through cytokines, chemokines, and leukocyte infiltration [15].

The patient in this case report was administered with dexamethasone for 3 days because a dengue-associated immune-mediated neurological disorder was suspected. In contrast, the patient in the first case report was administered methylprednisolone for 5 days. During the 2-month follow-up, the patient in the first case report improved in gait and ophthalmoparesis, and the brain lesion was resolved on MRI [8]. However, the GCS score of the present patient increased to 9 during the 1-month follow-up period, indicating partial neurological recovery. There are currently no specific therapies for dengue encephalitis [6,16]. Other possible causes of altered sensorium should be ruled out, and supportive management should be implemented [16]. For patients with dengue myelitis, acute disseminated encephalomyelitis, and dengue-associated neuro-ophthalmic infection, steroid therapy with pulses of intravenous methylprednisolone over several days is recommended. However, no randomised controlled trials have been conducted [6,16]. Therefore, future studies should focus on randomised controlled studies, which is necessary to determine the efficacy of this treatment regimen in patients with dengue encephalitis.

During the recovery phase, our patient had severe bleeding associated with refractory thrombocytopenia, as the platelet count did not start increasing until day 13 since fever onset and platelet transfusion did not increase the platelet count. Previous studies in adults with dengue showed that the platelet count increased to $>50{,}000/mm^3$ on day 8 since fever onset [3,4]. The present case had refractory thrombocytopenia, as the platelet count did not increase despite multiple administrations of platelet concentrate on days 10 to 14 since fever onset. According to the literature review (Table S3), several case reports of refractory thrombocytopenia have been reported in patients with dengue [17,18,19,20,21,22,23,24,25,26,27,28]. A summary of case reports showed that refractory thrombocytopenia in dengue could occur in both children and adults and was identified on day 14 or later since fever onset among most of the patients (9/11) [17–20,23–28]. The bone marrow aspiration/biopsy findings in dengue patients with refractory thrombocytopenia revealed normal or increased megakaryocytes (10/11) [17,19–21,23–28], but one patient (1/11) with multiple myeloma had hypocellular marrow [21]. The possible causes of thrombocytopenia in dengue include impaired platelet production in the bone marrow and immunologically accelerated platelet destruction [29].

The summary of case reports dealing with refractory thrombocytopenia in dengue (Table S3) revealed that most patients (16/17) [17,18,19,20,21,22,23,24,25,26,27,28] had clinical bleeding, and most of the patients with intracranial bleeding (3/4) died [20,23,27,28]. Therefore, a treatment regimen for an elevated platelet count is needed. Unfortunately, optimal times for identifying refractory thrombocytopenia and starting treatment in patients with dengue have not been clearly defined. In addition, there is no standard treatment recommendation for patients with refractory thrombocytopenia. The treatment regimens, including steroids, immunoglobulins, or thrombopoietic agents and their combinations, differed between case reports because clinical trials were unavailable (Table S3) [17,18,19,20,21,22,23,24,25,26,27,28]. Patients who responded to the treatment regimens recovered from refractory thrombocytopenia within 2–8 days [17,19,21,22,23,24,25,26,27,28]. However, two patients did not receive any treatment for refractory thrombocytopenia [18,20]. One patient had a longer platelet recovery duration (44 days since fever onset) [18], while the other died from massive intracranial bleeding [20]. In the phase II clinical trial, eltrombopag (a thrombopoietin receptor agonist) increased platelet count and stopped bleeding in patients with dengue and thrombocytopenia [30]. Therefore, the present patient was administered methylprednisolone with eltrombopag, and there was no bleeding, an increased platelet count, and a return of normal kidney function within 4 days. However, further studies are needed to determine the efficacy of this treatment in patients with dengue who have severe bleeding associated with refractory thrombocytopenia.

The present case study has some limitations, as the molecular and serological diagnosis for dengue and other common *Flaviviridae* in Thailand were performed on retrospective samples on days 5 to 11 since fever onset. Thereafter, blood samples were not collected to determine antibodies to *Flaviviridae* as the patients received blood and blood product transfusions nearly every day, which might have affected the results of serological testing. The RT-PCR for both JEV and ZIKV were not performed.

3. Conclusions

Dengue can cause infectious rhombencephalitis. Neurological disorders in dengue-associated rhombencephalitis can occur one week after fever onset or during the critical phase of dengue. In addition, refractory thrombocytopenia with severe bleeding occurs during the recovery phase of dengue. Further, methylprednisolone with a thrombopoietin receptor agonist could be an effective treatment to increase the platelet count and stop the bleeding.

Ethical approval statement

Written informed consent was obtained from the patient's legal guardian for the publication of this article.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17419.

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