CASE REPORT

Intravenous immunoglobulin for severe thrombocytopenia in secondary dengue

Vinod Kumar, Kartik Gupta, Manish Soneja, Ashutosh Biswas

Department of Medicine, All India Institute of Medical Sciences, New Delhi, India

Correspondence to
Dr Manish Soneja,
manishsoneja@gmail.com

Accepted 8 June 2018

SUMMARY

A 30-year-old woman with severe dengue presented on the sixth day of her illness with life-threatening thrombocytopenia, refractory to multiple platelet transfusions. Dengue IgM antibody and the non-structural-1 antigen tests as of day 3 were negative. The IgG antibody against the same was positive, suggesting a past episode of dengue. Since she had a history of menorrhagia prior to the current illness, a working diagnosis of idiopathic thrombocytopenic purpura was made, for which intravenous immunoglobulin (IVIg) was administered that led to a rapid rise in the platelet count with no adverse events. Subsequently, dengue IgM antibody repeated on day 6 came back positive, confirming dengue. This case report re-emphasises the potential use of IVIg in patients with severe thrombocytopenia in dengue.

BACKGROUND

Dengue causes significant morbidity and mortality in the tropical countries. In 2015, North India had the most recorded number of cases in the last decade.¹ The dengue virus has four different serotypes—DENV1, DENV2, DENV3 and DENV4. Fever with thrombocytopenia is the usual clinical presentation which may be complicated by haemorrhage and shock. Here we present a case of severe dengue with refractory thrombocytopenia that responded to intravenous immunoglobulin (IVIg).

CASE PRESENTATION

A 30-year-old married woman presented with a history of fever for 2 days. On day 3 of her illness, the patient became afebrile but started bleeding from the oral cavity and gums, and developed red spots over her trunk and lower limbs. At her first medical encounter on day 3, she had a platelet count of $17 \times 10^9/L$. The non-structural-1 (NS1) antigen and dengue IgM were negative, while dengue IgG was positive, suggestive of a past dengue infection. There was no improvement with single donor platelet transfusions and the lowest platelet count recorded was $1 \times 10^9/L$ on the fourth day.

The patient was referred to our hospital on the sixth day of illness. Her vital parameters were stable. There were petechiae and ecchymosis on the patient's abdomen and lower limbs (figure 1). She also had a wet purpura on the palate with active gum bleeding. On further questioning, it came to light that she had irregular and heavy menses in the past. There was no history of a

similar rash, abdominal pain, bleeding per rectum or blood transfusions in the past.

TREATMENT

Despite multiple platelet transfusions (single and random donor), there was no increase in the platelet count. Her history of menorrhagia, with negative NS1 antigen and IgM antibody for dengue, and refractory thrombocytopenia suggested a diagnosis of idiopathic thrombocytopenic purpura (ITP). She was administered IVIg at a dose of 2 g/kg body weight over 2 days.

OUTCOME AND FOLLOW-UP

With IVIg, an immediate rise in the platelet count was seen, with a count of $35 \times 10^9/L$, $78 \times 10^9/L$ and $130 \times 10^9/L$ at 12, 36 and 72 hours, respectively. The bone marrow aspirate and biopsy subsequently done were normal. The dengue IgM antibody test was then repeated on day 7 of illness which came back positive. We then revised the diagnosis to severe secondary dengue infection. The patient was discharged in a stable condition without any adverse events. The platelet count was $185 \times 10^9/L$ and $230 \times 10^9/L$ at 2 and 6 weeks postdischarge, respectively.

DISCUSSION

Acute febrile illness with thrombocytopenia in an endemic area should raise a suspicion of dengue. Common differentials of this clinical syndrome in a tropical country are malaria, leptospirosis and scrub typhus. Many chronic haematological conditions are unmasked during the evaluation for febrile illness(es) as this is often the first medical contact of many patients in their life.² Though we made a provisional diagnosis of ITP based on the history and consequently treated her with IVIg, she eventually turned out to have severe secondary dengue infection.

The thrombocytopenia in dengue is multifactorial: decreased production by the suppressed bone marrow, increased consumption due to lysis by the complement system and increased apoptosis through formation of platelet antibodies are some common causes listed.^{3–5} Persistent thrombocytopenia in dengue has been reported earlier though the mechanisms remain unclear.^{6,7}

A repeat dengue infection with a heterotypic dengue virus is associated with an increased formation of the platelet-associated-IgM (PAIgM) and IgG (PAIgG) antibodies in the acute phase.^{8,9} There

© BMJ Publishing Group Limited 2018. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Kumar V, Gupta K, Soneja M, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224542

Figure 1 Ecchymotic patches over the lower abdominal wall and thigh of the patient.

is an inverse correlation with an increased production of PAIgM and PAIgG antibodies associated with a lower platelet count.⁸ The platelets coated with these antibodies may also react with the virus-infected endothelial cells, causing increased vascular permeability and dengue haemorrhagic fever.

Real-time PCR for the viral RNA or the NS1 antigen detection test can help establish a diagnosis of dengue in the first week of the illness. The NS1 antigen detection test has a sensitivity of 90% and 60%–80% in primary and secondary infections, respectively.^{10–12} In primary infection, IgM antibody can be detected in the serum as early as the fourth day of the illness; IgG antibody formation starts after 7 days of onset of the illness and thereafter persists life-long. IgG antibody can thus be used for the diagnosis of a previous infection.^{13 14} In the secondary infection, the IgG antibody rises rapidly after the onset of fever, and the IgM antibody response may be delayed or be negligible.^{1 15} In our case, the initial test for IgG antibody was positive with negative IgM antibody and NS1 antigen on the third day of illness, indicative of a past infection. Later, on the seventh day of the illness, the IgM antibody test was positive, suggesting a secondary dengue infection.

IVIg has multiple modes of action including suppression of the complement activation and antibody production.^{16 17} It saturates the Fc receptors on macrophages, inhibits the actions of the inflammatory mediators and generation of the membrane attack complex (C5b-C9). Suppressed inflammation minimises destruction of the platelets and reduces vascular permeability.

There is limited literature available on the use of IVIg in dengue. There are some case reports where IVIg has been used successfully for persistent thrombocytopenia in dengue.^{6 18} There are few randomised control trials (RCT) with a very small sample size evaluating the role of immunoglobulins in dengue infection. In secondary dengue infection with thrombocytopenia, Dimaano and colleagues failed to demonstrate improved platelet counts with IVIg.¹⁹ This trial had only 31 subjects, studied the paediatric age group (mean age ~15 years) and excluded patients with shock or bleeding. Another RCT (n=30), evaluating the role of anti-D immunoglobulin in dengue with thrombocytopenia, showed a significant early rise in platelet count in the treatment arm.²⁰ There was, however, no significant difference in the platelet counts at the time of discharge. Similar early increase in platelet count with the use of anti-D immunoglobulin has

been demonstrated by de Castro and colleagues.²¹ A dedicated RCT, with a large sample size, should evaluate the role of IVIg in dengue with thrombocytopenia.

Learning points

- Secondary dengue may have a decreased sensitivity of non-structural-1 antigen detection and a delayed IgM response. Detection of IgG antibody may help in early diagnosis.
- Intravenous immunoglobulin (IVIg) is a potential life-saving agent in refractory thrombocytopenia in secondary dengue infection.
- Use of IVIg should be further evaluated in well-controlled randomised trials.

Contributors VK: report writing, data collection and patient management. KG: review of literature and data collection. MS: patient management decisions and report writing and finalisation. AB: patient management decisions and guidance.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 WHO. Dengue guidelines for diagnosis, treatment, prevention and control: new edition. <http://www.who.int/rpc/guidelines/9789241547871/en/> (accessed 15 Dec 2017).
- 2 Gulati S, Maheshwari A. Dengue fever-like illnesses: how different are they from each other? *Scand J Infect Dis* 2012;44:522–30.
- 3 La Russa VF, Innis BL. Mechanisms of dengue virus-induced bone marrow suppression. *Baillieres Clin Haematol* 1995;8:249–70.
- 4 Rosenfeld SJ, Young NS. Viruses and bone marrow failure. *Blood Rev* 1991;5:71–7.
- 5 Phanichyakarn P, Pongpanich B, Israngkura PB, et al. Studies on Dengue hemorrhagic fever. III. Serum complement (C3) and platelet studies. *J Med Assoc Thai* 1977;60:301–6.
- 6 Kumar P, Charaniya R, Ghosh A, et al. Intravenous Immunoglobulin Responsive Persistent Thrombocytopenia after Dengue Haemorrhagic Fever. *J Clin Diagn Res* 2016;10:OD10–OD11.
- 7 Kohli U, Saharan S, Lodha R, et al. Persistent thrombocytopenia following dengue shock syndrome. *Indian J Pediatr* 2008;75:82–3.
- 8 Oishi K, Inoue S, Cinco MT, et al. Correlation between increased platelet-associated IgG and thrombocytopenia in secondary dengue virus infections. *J Med Virol* 2003;71:259–64.
- 9 Saito M, Oishi K, Inoue S, et al. Association of increased platelet-associated immunoglobulins with thrombocytopenia and the severity of disease in secondary dengue virus infections. *Clin Exp Immunol* 2004;138:299–303.
- 10 Hermann LL, Thaisomboonsuk B, Poolpanichupatam Y, et al. Evaluation of a dengue NS1 antigen detection assay sensitivity and specificity for the diagnosis of acute dengue virus infection. *PLoS Negl Trop Dis* 2014;8:e3193.
- 11 Sekaran S L, Ew C, Subramaniam G, et al. Sensitivity of dengue virus NS-1 detection in primary and secondary infections. *Afr J Microbiol Res* 2009;3:105–10.
- 12 Kumarasamy V, Wahab AH, Chua SK, et al. Evaluation of a commercial dengue NS1 antigen-capture ELISA for laboratory diagnosis of acute dengue virus infection. *J Virol Methods* 2007;140:75–9.
- 13 Shu PY, Chen LK, Chang SF, et al. Comparison of capture immunoglobulin M (IgM) and IgG enzyme-linked immunosorbent assay (ELISA) and nonstructural protein NS1 serotype-specific IgG ELISA for differentiation of primary and secondary dengue virus infections. *Clin Diagn Lab Immunol* 2003;10:622–30.
- 14 Falconar AK, de Plata E, Romero-Vivas CM. Altered enzyme-linked immunosorbent assay immunoglobulin M (IgM)/IgG optical density ratios can correctly classify all primary or secondary dengue virus infections 1 day after the onset of symptoms, when all of the viruses can be isolated. *Clin Vaccine Immunol* 2006;13:1044–51.
- 15 Sa-Ngasang A, Anantapreecha S, A-Nuegonpipat A, et al. Specific IgM and IgG responses in primary and secondary dengue virus infections determined by enzyme-linked immunosorbent assay. *Epidemiol Infect* 2006;134:820–5.
- 16 Dalakas MC. Mechanisms of action of IVIg and therapeutic considerations in the treatment of acute and chronic demyelinating neuropathies. *Neurology* 2002;59:S13–21.
- 17 Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 2001;345:747–55.

- 18 Ostronoff M, Ostronoff F, Florêncio R, *et al.* Serious thrombocytopenia due to dengue hemorrhagic fever treated with high dosages of immunoglobulin. *Clin Infect Dis* 2003;36:1623–4.
- 19 Dimaano EM, Saito M, Honda S, *et al.* Lack of efficacy of high-dose intravenous immunoglobulin treatment of severe thrombocytopenia in patients with secondary dengue virus infection. *Am J Trop Med Hyg* 2007;77:1135–8.
- 20 Pannu AK, Bhalla A, Singhal M, *et al.* Safety and Efficacy of a Single Dose of Anti-D (WinRho®) in Severe Thrombocytopenia Secondary to Dengue Virus Infection. *Indian J Crit Care Med* 2017;21:80–4.
- 21 de Castro RA, de Castro JA, Barez MY, *et al.* Thrombocytopenia associated with dengue hemorrhagic fever responds to intravenous administration of anti-D (Rh(0)-D) immune globulin. *Am J Trop Med Hyg* 2007;76:737–42.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow