

Permanent visual impairment in dengue fever following platelet transfusion: A series of 5 cases

Dear Editor,

Dengue fever (DF) is endemic in India and Singapore, and also causes frequent epidemics. Dengue virus belongs to the *Flavivirus* genus of the family *Flaviviridae* and its members include the 4 antigenically related serotypes of dengue virus (DENV 1–4). It is transmitted to humans through the bite of infected female *Aedes aegypti* mosquitoes, and is characterised by an acute onset of fever associated with symptoms of malaise, headache, muscle aches, retro-orbital pain, joint pain, abdominal discomfort, rash and bleeding diathesis.

Thrombocytopenia, a major feature of DF, results from decreased platelet production from bone marrow suppression or increased platelet destruction. Prophylactic platelet transfusion is a common practice to prevent clinical bleeding in adults with dengue and thrombocytopenia. However, transfusion of blood products may be detrimental to patients given the risks of fluid overload, transmission of infectious diseases and transfusion reactions.

Ocular findings associated with DF are subconjunctival haemorrhage, vitreous haemorrhage, retinal haemorrhage, cotton wool spots, central and branch retinal artery occlusion, central scotoma, papilloedema, optic neuropathy, retinal vasculitis, retinitis, retinal pigment epithelium mottling, foveolitis, choroidal effusion, exudative retinal detachment, anterior uveitis, endogenous endophthalmitis and panophthalmitis.¹

Panophthalmitis is a rare complication, with only 7 cases reported following platelet transfusion in DF in the literature.²⁻⁷ We report 5 cases of unusual complication of DF causing panophthalmitis, leading to rapidly progressive and painful visual loss shortly after receiving platelet transfusion. These 5 cases were referred from 5 different centres to our tertiary eye centre for ocular evaluation. As we are not aware of the prevailing practices in those centres, we are unable to comment on the rationale for platelet transfusion. These 5 cases occurred over a 6-month period from July to December 2019. Table 1 summarises these 5 cases.

Platelets are vulnerable to bacterial growth as they are stored at room temperature for up to 5 days, whereas other blood components are refrigerated or frozen. Gram-positive bacteria (e.g. *Staphylococcus*

sp.) found on the skin are the most frequent contaminants of platelet units. Gram-negative bacteria (e.g. *Serratia*, *Enterobacter* or *Salmonella* sp.) account for more severe and fatal infections, and are attributed to donor bacteremia or contamination during product processing.⁸ Kuehnert et al. estimated that the rate of transfusion-transmitted bacteremia (in events/million units) was 9.98 for single-donor platelets, 10.64 for pooled platelets and 0.21 for red blood cell units.⁸ The US Food and Drug Administration requires only fatal complications of blood collection or transfusion to be reported. Antimicrobials and anti-inflammatory agents in transfused populations may account for the partial masking of symptoms that are normally associated with sepsis.⁸

A study by Lee et al. on adult dengue patients in Singapore found that the occurrence of internal bleeding after platelet transfusion was slightly more common albeit statistically insignificant.⁹ More mucosal bleeding after platelet transfusion in transfused patients (18.5%) versus non-transfused patients (9.3%) was reported. In the transfused patients, platelet count increased significantly more the next day after platelet transfusion than in the non-transfused patients followed by a slow increase over the few days. Among the transfused patients, liver enzyme levels (aspartate aminotransferase and alanine aminotransferase) were found to be higher, 2 patients developed liver failure and 1 patient developed renal failure.⁹

Studies in India showed that acute respiratory distress syndrome, fever, longer duration of fever, longer duration of hospitalisation and slower recovery of platelets were more common in transfused patients compared to the control group.¹⁰

Approaches to reduce the incidence of transfusion-transmitted bacterial infection include expansion of donor screening, improved donor skin antisepsis, discarding an initial aliquot of donated blood to reduce skin contaminants, limitation of component storage time or lowering storage temperature, diagnostic screening of components and photochemical decontamination.⁸

Frequency of blood component bacterial contamination associated with transfusion reaction (the BaCon Study)⁸ was initiated to better estimate their occurrence. Results showed no significant

Table 1. Summary of our 5 cases

Case no.	Age/sex	Symptoms	Systemic treatment	Interval between fever and ocular symptoms	Ocular symptoms	Ocular signs at presentation	Systemic investigations	Ocular imaging (B-scan)	CT/MRI findings	Treatment
1	26/male	Fever (5 days), bleeding from gums	Platelet transfusion, IV methylprednisolone	5 days	Sudden decrease in vision in BE associated with pain	BE: NPL, severe proptosis, subconjunctival haemorrhage, corneal blood staining, total hyphaema, high digital IOP, restricted ocular motility	Dengue NSI positive, platelet count of 16,000/mm ³	Vitreous debris, thickening of the scleral coats, with fluid in Sub Tenon's space	CT of orbit: vitreous haemorrhage with mild thickening of ocular coats. RE: a focal thinning of ocular coat on nasal aspect with impending rupture was visible	Intravenous antibiotics and anti-glaucoma agents
2	30/male	Fever (4 days)	Platelet transfusion (3 units)	4 days	Pain and sudden loss of vision in RE	RE: NPL, severe proptosis, subconjunctival haemorrhage, adherent leucoma, total hyphaema, high digital IOP, restricted ocular motility. LE: WNL	Dengue NSI positive, platelet count of 12,000/mm ³	Thickening of the scleral coats, with fluid in Sub Tenon's space in RE	MRI of orbit: deformed globe with deformed anterior chamber. Lens was subluxated thickened globe wall. Vitreous haemorrhage was present. Peribulbar inflammatory soft tissue was present with thinning of the globe wall on temporal aspect with epibulbar/episcleral abscess collection with impending rupture/ruptured globe	Intravenous antibiotics and anti-glaucoma agents
3	55/female	Fever, nausea, abdominal pain, generalised weakness	Platelet transfusion, IV antibiotics, PPI, anti-emetics, steroids and other supportive measures	2 weeks	Sudden onset pain, swelling and decrease in vision in RE	RE: PL, eyelid oedema, orbital swelling, hazy cornea, organised hyphaema, very shallow AC, ocular motility restricted. LE: WNL	Dengue NSI positive	Multiple hyperdense dot echoes in vitreous cavity, severe choroidal thickening, positive T-sign	MRI of brain and orbit with contrast: right-sided proptosis with inflammatory changes in retro-orbital soft tissues. Associated preseptal oedema. Thickening of RE globe wall. Periscleral inflammatory changes present	Tapering oral steroids

Table 1 Summary of our 5 cases (Cont'd)

Case no.	Age/sex	Symptoms	Systemic treatment	Interval between fever and ocular symptoms	Ocular symptoms	Ocular signs at presentation	Systemic investigations	Ocular imaging (B-scan)	CT/MRI findings	Treatment
4	45/male	Fever, generalised weakness	Platelet transfusion, IV fluids	5 days	Sudden onset pain and redness in BE	RE: NPL, LE: PL, BE: dilated episcleral vessels, conjunctival congestion, opaque cornea, IOP RE: 28mmHg, LE: 20mmHg	Dengue NSI positive	RE: subretinal moderate to high reflective echoes, suprachoroidal echoes, LE: thickening of the scleral coats, with fluid in Sub Tenon's space	MRI: bilateral chorioretinitis with retro-orbital oedema	BE lensectomy and vitrectomy, antibiotics, steroids
5	15/male	Fever (1 week), vomiting, giddiness	Platelet transfusion, IV antibiotics, IV fluids	6 days	Sudden onset pain and swelling in RE	RE: NPL, RE: proptosis, lid oedema, conjunctival congestion, corneal blood staining, hyphaema, hypotonous	Dengue NSI positive, eye swab and blood culture (no growth)	RE: deformed globe, posterior wall thickening and oedematous periorbital soft tissue swelling, subtle internal echoes in posterosuperior aspect of globe suggesting abscess	MRI: RE with thickened ocular coats, abscess in orbit, thickening in preseptal and periorbital soft tissues indicating panophthalmitis of RE	Intravitreal antibiotics, topical steroids, RE evisceration

AC: anterior chamber; BE: both eyes; CECT: contrast enhanced computed tomography; IOP: intraocular pressure; IV: intravenous; LE: left eye; MRI: magnetic resonance imaging; NPL: no perception of light; NSI: nonstructural protein 1; PPI: proton pump inhibitor; PL: perception of light; RE: right eye; VH: vitreous haemorrhage; WNL: within normal limits

difference between the rates of transfusion-transmitted bacterial infection associated with single donor platelets and those associated with pooled platelets.¹¹

Most DF-related ocular involvements are limited to the posterior segment, and manifest in the form of retinal vasculitis, retinitis, macular oedema or optic neuropathy. Endogenous endophthalmitis have been reported in DF and following platelet transfusion.⁵ Panophthalmitis associated with DF has been rarely reported.¹

Panophthalmitis, a rare complication of DF, is an acute inflammation of all the coats of eyeball including intraocular structures. In normal circumstances, the blood ocular barrier provides a natural resistance against invading organisms. Panophthalmitis/endophthalmitis may result in secondary to inflammatory or immune response to dengue virus; it may also lead to microorganisms crossing the blood ocular barrier to cause septic foci in the retina, which then spreads to the vitreous and anterior segments. Disintegration of the endothelial cells caused by antibodies against nonstructural protein 1 (NS1) antigen facilitates direct entry of the bacteria into the uveal and retinal circulation, causing septic foci and secondary endophthalmitis.

Five of the previous 7 published cases of dengue panophthalmitis had history of platelet transfusion. Five cases had unilateral involvement and 2 had bilateral involvement. The vision could not be salvaged in any of the affected eyes. Microorganisms isolated from the eye swab included gram-positive cocci with no growth, and *Bacillus cereus* was isolated from the eviscerated sample of the eye.^{4,5}

In our series of 5 cases, the patients developed panophthalmitis shortly after receiving platelet transfusion and were referred to our tertiary eye centre. Average onset duration of complication was 5.5 days after transfusion (range of 4–7 days). Three cases had unilateral and 2 bilateral involvements respectively.

In 2 of our cases the presentation of panophthalmitis was initially atypical, hence an initial diagnosis of retrobulbar haemorrhage was made before referring to our centre. Both patients on ultrasound B scan had vitreous debris and thickening of the scleral coats, with fluid in Sub Tenon's space in the affected eyes and were blind. All the patients had undergone blood culture before referral to us with no reported growth of pathological organisms. At our tertiary eye centre, Gram's stain and potassium hydroxide mount and culture of the conjunctival swab did not show any microorganisms in all the 5 cases. Cases 4 and 5

underwent vitreous sampling and no growth of pathological organism was detected.

The crux in the management of dengue patients is maintaining good hydration, monitoring for any overt bleeding, alongside periodic checking on peripheral pulses and blood pressure with serial estimation of haematocrit and platelet counts.¹² Supportive care consists of bed rest, fluid therapy and fever and pain relief medications.

The risk of transfusion-related adverse effects such as anaphylaxis, transmission of blood-borne infections and acute lung injury always exists with transfusion of blood products, including platelets. Prophylactic platelet transfusion has no added advantage over supportive care. The lack of efficacy of prophylactic platelet transfusion, combined with higher risk of adverse events, leads us to discourage the practice of routine prophylactic platelet transfusion in adult dengue.

Clinicians and ophthalmologists should be aware of this vision-threatening complication of DF for early recognition and prompt treatment. Vision could not be salvaged in any of the affected eyes in our 5 cases. Therefore, caution should be exercised while considering prophylactic platelet therapy in patients with DF.

Ophthalmological examination should be routinely done in all patients with DF. Patients with dengue who present with endophthalmitis or panophthalmitis should be aggressively managed, and samples (aqueous/vitreous or eviscerated material) should be subjected to standard microbiological tests to investigate for offending organisms to tailor the therapy accordingly.

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