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Case Report

Management of Dengue Fever with Severe Thrombocytopenia in a Patient While on Warfarin: A Case Report

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Abstract

Background: Dengue fever is the most prevalent mosquito borne viral disease in South and Southeast Asia. Managing a dengue infection with severe thrombocytopenia is a challenge especially when complicated by other comorbidities. We report a patient with dengue fever and thrombocytopenia who is on warfarin due to atrial fibrillation with severe mitral regurgitation while awaiting a mitral valve replacement.

Case Presentation: A 40 year- old Sri Lankan male with severe mitral regurgitation presented with fever, retro orbital headache, arthralgia and myalgia for 3 days found to have positive dengue NS 1 antigen on day 3 of fever. He was on warfarin 7mg daily at that time which was commenced for atrial fibrillation with severe mitral regurgitation. He did not have any systemic symptoms or bleeding manifestations. Lowest platelet count detected during the illness was 15,000/µL. In managing the patient, the risk of bleeding had to be balanced against the risk of thromboembolism without anticoagulation. Warfarin was withheld when the platelet count dropped to less than 100,000/µL and restarted when it recovered above 50,000/µL. The patient was off anticoagulation for 07 days without complications.

Conclusions: We managed this patient with close observation for bleeding as well as for thromboembolic events and continuous risk benefit assessments of management decisions. However, experience with one patient may not be generalized to others. Therefore, sharing clinical experience in managing such difficult patients with dengue fever could be very useful for clinicians who might involve in the care of similar patients.

Keywords: Dengue Fever; Severe Thrombocytopenia; Anticoagulation

Background

Dengue fever is a potentially lethal illness that is universally prevalent in the tropics [1]. Dengue hemorrhagic fever is characterized by a 'leakage phase' (or critical phase) usually lasting 48 hours following an initial febrile phase [2,3]. During the leakage phase, an increase in capillary permeability leads to extravasation of fluid and haemoconcentration. During the latter part of febrile phase and early leakage phase (or even later), there is a steady drop in platelet count. Some patients with dengue fever will develop severe thrombocytopenia during the course of the illness even without going into a critical phase and the platelet count does not necessarily indicate the severity of infection [2,3]. At occasions, it can drop as low as 500/µl in previously healthy individuals (normal platelet count in a healthy adult: 150,000-400,000/µl). The exact mechanism of this drop is unclear but presumed to be immunological. The low platelet count leaves the patient at a significant risk of spontaneous bleeding. The management is further complicated by pre-existing co-morbidities that interfere with the usual therapeutic guidelines. Use of oral anticoagulants is one such situation where management of dengue fever could be challenging [4,5]. We report a patient with severe dengue infection with very low platelet counts without bleeding manifestations who was on anticoagulation with warfarin for atrial fibrillation with severe mitral regurgitation awaiting prosthetic mitral valve replacement.

Case Presentation

A fifty one year old Sri Lankan male, presented with fever for three days and arthralgia, myalgia and retro orbital headache. There were no other systemic symptoms to suggest any focus of infection. He had mitral regurgitation following papillary muscle rupture due to a myocardial infarction one year ago complicated with atrial fibrillation for which he was on anticoagulant therapy with warfarin. His target PT INR (Prothrombin Time International Normalized Ratio) of 2-3, maintained with 7mg of warfarin per day. His other medications included; digoxin, and a combination of hydrochlorothiazide and furosemide. His 2D echocardiography done on August-2016 revealed grade 1V mitral regurgitation with left ventricular ejection fraction of 60%. On admission, he was hemodynamically stable with an irregularly irregular pulse at a rate of 76 beats per minute and a blood pressure of 110/60mmHg. All the peripheral pulses were felt and capillary refilling time was <2 seconds. On auscultation, there was a pan-systolic murmur at cardiac apex with radiation to axilla. Respiratory system and the rest of the system examinations were

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Table 1: Laboratory investigations.
A summary of investigation results of the patient during the illness.

	D2	D3	D4	D5	D6	D7	D8	D9	D10
WBC (*106/L)	5.9	5.4	5.2	5	4.8	5.8	6.2	8.2	8.8
HCT%	42	42	41.90%	41	42	40	39	39	37.9
HB (g/Dl)	14	14	14.2	14	14	14	14	14	13.5
PLT (*106)	127	98	77	45	27	14	15	32	72
INR		1.3				1.1			
AST(U/L)		59				79			
ALT(U/L)		48				55			

D: Day of Fever; WBC: White Blood Cells; HCT: Hematocrit; PLT: Platelet Count; INR: International Normalization Ratio; AST: Asparate Transaminase; ALT: Alanine Transaminase

normal. Throughout the course of the illness he had no postural drop in blood pressure or a narrowed pulse pressure to indicate any significant intravascular volume depletion.

The provisional diagnosis of dengue fever was made which subsequently confirmed by the positive dengue NS 1 antigen done on day 3 of his illness. His admission coincided with a dengue epidemic in the area. However, measures were taken to exclude an alternative infection like infective endocarditis. Strict monitoring of vital parameters with careful observation for any bleeding manifestations or thromboembolic phenomena was performed throughout the course of the illness.

His full blood count on day 3 of the illness revealed total white cell count of 5.9*103/uL, Hemoglobin (Hb) of 13.8g/dl and platelet count of 127*103/uL. Subsequent full blood counts showed a leucopenia and a trend of dropping platelet counts. On day 3 after admission (date of admission taken as day 0), her fever subsided but there was no evidence of fluid leaking clinically or ultrasonically. The platelet count that was already low was expected to hit a nadir between days 4-5. The patient was at the highest risk of internal haemorrhage during that time. The usual management protocol at this time calls for optimization of fluid intake and observation for bleeding manifestations and fluid leakage. Prophylactic platelet transfusions are discouraged unless there is a life threatening haemorrhage. However, this particular patient was at high risk of bleeding because of anticoagulation. Stopping anticoagulation had the potential complication of thromboembolic phenomena while continuing warfarin had the risk of a torrential internal haemorrhage aided by an already low platelet count. In the absence of guidelines and only one previously reported similar case, we managed the patient with institutional expert opinion.

Fever was treated symptomatically with paracetamol. Frusemide and hydrochlorothiazide was temporarily withheld since admission. Once the platelet count dropped below 100×103/µl, warfarin was withheld. Digoxin was continued at its usual dose of 0.25µg two times daily. The rationale for stopping warfarin was to keep the patient off it during the period of significant thrombocytopenia where the risk of life threatening bleeding is highest. However, as warfarin has a long half-life of 3-5 days, it was necessary to stop it at least two to three days before the anticipated onset of significant thrombocytopenia. The plan was to restart warfarin as soon as the platelet count was back within 'safe' margins. On him we stopped warfarin from day 3 of the illness where the platelets dropped to 98,000/uL and restarted warfarin on day 10 of the illness once platelet had risen to >50,000/uL. During that period he neither had significant bleeding nor thromboembolic phenomena.

Discussion

The incidence of dengue is rising in many countries and it remains a life threatening illness in the tropics [1,2]. During dengue epidemics, large numbers of patients (approximately thousands) in all age groups are affected. The natural course of illness and the management approach can be complicated by underlying co-morbidities of patients.

As mentioned above, this patient's management during the initial phase of the illness was complicated by two conflicting life threatening conditions; a) risk of massive internal haemorrhage or an intracranial bleed due to dengue induced thrombocytopenia and b) the need to continue warfarin therapy to avoid a thromboembolic stroke. Therefore, withholding warfarin was a precarious balancing act to allow just enough time for the thrombocytopenia to recover and not too long for a thromboembolic complication such as an ischemic stroke [4]. Decision making was further complicated by the long half- life of warfarin [4,5]. In the absence of guidelines and rarity of even published case reports in this regard, it was arbitrarily decided that the risk of bleeding would be significant when the platelet count dropped below 50,000/µl. Warfarin had to be stopped well before this mark [4]. It is difficult to predict the rate of drop in platelet count in dengue as in some patients it drops drastically during the critical phase. Adding to the confusion, the critical phase is not synonymous with the period of rapid platelet drop. In other words, the platelet count may continue to fall or fail to rise even after the critical phase is over. Critical phase is only a surrogate marker for the period of rapid platelet drop. The critical/leakage phase is more correctly recognized by presence of a pleural effusion or as cites (clinically or radiologically). It is assumed that when the platelet count drops below 100,000/µl, the patient will go in to the leakage (critical) phase in the next 24 hours. Taking all in to account, we stopped warfarin when the platelet count approached 100,000/µl and anticipated an interval of at least 48 hours before it dropped below 50,000/µl [4]. The predictions were reasonably accurate and gave us the expected time window for the action of warfarin to wear off. Although our patient did not have any evidence of fluid leakage it took two days for the platelets to drop to less than 50,000/uL (it was 45,000/uL on day 5) since the time we stopped warfarin on day 3 (98,000/uL).

Prophylactic platelet transfusions are not recommended in dengue as per national guidelines [1]. We preferred the platelet count to be above 50,000/µL to restart warfarin where 7 days had lapsed without anticoagulation in our patient. More importantly he had neither life threatening bleeding manifestations nor thromboembolic complications during the period of illness.

Management of patients with dengue fever while on anticoagulation is not touched in the current guidelines [1,2]. We came across only one case report locally describing the experience in managing a patient with dengue fever who was also on anticoagulation [4]. Our case will add to the sparse literature of managing such a patient which is an uncharted territory among most of us involved in caring patients with dengue fever.

Dengue is a life threatening illness affecting thousands of patients including those with co-morbid medical conditions, during epidemics. One such important co-morbid condition could be being on anticoagulation like in our case. Guidelines on managing such patients are nonexistent in published guidelines [1,2]. Our experience with this patient stresses that careful monitoring and planning of management ahead of projected changes in platelet counts can be lifesaving. However, the same protocol may not be valid for a second patient. Therefore it is important that clinicians share their experiences in managing such difficult patients.

Consent

Written informed consent was obtained from the patient for the publication of this case report.

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