Cause of Upper Gastrointestinal Tract Bleeding in Dengue Hemorrhagic Fever Patient

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ABSTRACT

Dengue fever is an acute mosquito-transmitted disease caused by the dengue fever virus which had clinical manifestations range from fever to severe hemorrhage, shock, and death.[1] There were 500,000 cases of dengue hemorrhagic fever and 25,000 deaths due to dengue annually worldwide. Bleeding is one of the major problems encountered in dengue fever. The reported prevalence of upper gastrointestinal bleeding in dengue patients varies from 5% to 30%. The pathogenesis of hemorrhage could be multifactor and include vasculopathy, platelet deficiency, and dysfunction, and blood coagulation defects. We presented here a case of 27 years-old male patient who had clinical manifestation of hematemesis on his third day of fever.

Keywords: GI tract, bleeding, DHF

INTRODUCTION

Dengue Fever (DF) is an acute mosquito-transmitted disease caused by the dengue fever virus of the family Flaviviridae, the most common cause of arboviral disease in the world. Clinical manifestations of dengue infection range from fever, headache, arthralgia, myalgia and skin rash, to severe hemorrhage, shock, and death.[1] It is estimated that there are 100 million cases of dengue infection, 500,000 cases of dengue hemorrhagic fever and 25,000 deaths due to dengue annually worldwide.[1]

In South East Asia, Dengue Hemorrhagic Fever (DHF) has been recognized for approximately 40 years. The vast majority of the cases are reported from Thailand, Indonesia, and Vietnam, which have very comprehensive surveillance systems. Per decade, the number of DHF cases has increased-from a mean of 50,000 per year in the 1970s to 165,000 in the 1980s and 200,000 in the 1990s.[2]

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Bleeding, one of the major problems encountered in DF, contributes to a worsening morbidity. The toxic hemorrhagic state appears during the third to fifth day of the illness, following the onset of fever, followed by convalescent stage. The most common hemorrhagic manifestations are epistaxis, skin hemorrhages, and gastrointestinal hemorrhages.[1]

The reported prevalence of upper gastrointestinal bleeding in dengue patients varies from 5% to 30%. Wang JY et al, found 11.8% of DF patient developed gastrointestinal hemorrhage with manifestation of haematemesis and/or melena.[3] Yi-Chun et al, identified 97 (8.4%) among 1,156 dengue patients had complications of upper gastrointestinal (GI) bleeding during hospitalization.[3] The endoscopic findings included hemorrhagic (and/or erosive) gastritis in 67% of the patients, gastric ulcer in 57.7%, duodenal ulcer in 26.8% and esophageal ulcer in 3.1.[1]

Most of the dengue patient who developed upper gastrointestinal bleeding had gastric ulcer or duodenal ulcers; superficial and hemorrhagic gastritis are other relevant endoscopic findings. Fifty percent patients had past history of peptic ulcers symptoms, whereas the other 50% were not. Dengue infection is a precipitating factor in inducing peptic ulcer bleeding because of hemostatic derangements.[4]

The pathogenesis of hemorrhage could be multifactor and include vasculopathy, platelet deficiency, and dysfunction, and blood coagulation defects. Most upper GI bleeding occurs on the fourth day after the onset of fever. In addition, almost all of dengue patients recovered after 7-14 days. Close monitoring of vital signs and hematocryte to evaluate the severity hemorrhage is mandatory to reduce morbidity. However, this acute disease will soon subside, and platelet count and function will spontaneously return to normal.[1]

However, the pathogenic mechanism of dengue virus (DV)-induced hemorrhage awaits clarification. A recent research "Both virus and tumor necrosis factor alpha are critical for endothelium damage in a mouse model of dengue virus-induced hemorrhage" reveals that high viral titer, macrophage infiltration, and tumor necrosis factor alpha (TNF-α) production in the local tissues are three important events that lead to hemorrhage.[5]

In this report, a 27 years-old male patient presented with hematemesis on his third day of fever. Further examination confirm positive serum dengue antibody. This is a case demonstration to illustrate feature of GI tract bleeding in DHF patient.

CASE ILLUSTRATION

A 27 years old male, had twice hematemesis just an hour prior admission. The amount of blood was about one cup (200 cc). Preceded by nausea and epigastric pain, the emesis were bright red, mixed with the food he just ate. He had sudden onset of fever 3 days before admission, relieved by antipyretic. He was taking paracetamol and amoxicillin. He also complained of headache, joint and muscular pain. There was melena but no previous bloody hematemesis, epistaxis, nor bleeding gums. He admitted taking Indonesian traditional herbs called *jamu beras merah* two glasses a day for two days, and admitted drink alcohol 2 years ago, but had stopped for two years. There was no previous history of gastritis nor jaundice. His sister was recently hospitalized for DHF.

His physical examination revealed moderate illness, compos mentis, blood pressure 110/80 mmHg, heart rate 120 beat/minutes, respiration rate 20 times/ minutes, and fever, temperature 38.4°C. The tourniquet test was positive.

Unless epigastric pain, other physical condition was unremarkable. Specifically no rash, conjunctiva injection, stigmata of neither cirrhosis nor jaundice was noted. Rectal examination was performing and reveals a mass at anal mucosa. It was supple and aches and no black stool was found. Laboratory findings were hemoglobin 13.8 g/dL, hematocryte 39%, leukocytes 7,200/μL, platelet count 153,000/uL, leukocyte differential count 0/1/2/81/15/1, blood sedimentation rate 10 mm/hour, urea 19 mg/dL, creatinin 1.4 mg/dL, total protein 6.7 g/dL, albumin 4.5 g/dL, globulin 2.2 g/dL, random balance sugar 127, sodium 133 meq/L, potassium 3.4 meq/L, and chloride 98 meq/L. Urinalysis were normal. Patient's chest X-ray was clear. Based on these data, we conclude the problems were hematemesis melena, DHF grade 1, electrolyte disturbances and internal hemorrhoid.

The patient was not allowed to take food or drinks and Nasogastric Tube (NGT) was placed. The liquid from showed bright, red blood or blood clots. Then, NGT was gently lavaged with room temperature water every six hour. Intravenous access was obtained, with infusion of crystalloid. Proton pump inhibitor, sistenol, sucralfat, and ondansentron were administered.

About 24 hours later the NGT came out clear and the patient started enteral nutrition. The patient was then planned for the evaluation for the cause of hematemesis by upper GI tract endoscopy. The Complete Blood Count (CBC) was checked every 12 hours and close monitoring of vital sign was obtained. On second day of hospitalization, patient complaint passaging of bright red blood from the rectum not intermixed with formed stool. The CBC were hemoglobin 15.8 g/dL, hematocryte 43.8%, leukocytes 2,100/ μL and platelet count 64,000/μL, prothrombin time 15.2 second (C:12.2), activated prothrombin time 44.2 second (C: 30.1), bleeding time 2 second, clotting time 11 second, fibrinogen 122 and D-dimer 700. IgG and IgM anti dengue were both negative. On day 5, the patient had no longer fever, and the CBC were hemoglobin 16.1 g/dL, hematocryt 45.1%, leukocytes 4,000/μL and platelet count 18,000/μL. IgG anti dengue was positive at day 7 (day 10 of illness). The upper GI endoscopy was performed on May 14th showed esophagitis and mild erosive gastritis. The pathology anatomy results came out on May 21st revealed a non-atrophic chronic gastritis and no *Helicobacter pylori* was found.

DISCUSSION

Hematemesis in this patient was thought to be due to erosive gastritis cause by the traditional herbs he had been taking. In a retrospective study about the causes of upper gastrointestinal bleeding in Cipto Mangunkusumo hospital, the cause of upper gastrointestinal bleeding was non variceal (66.5%) and variceal (33.5%). Among non variceal, ulcer and erosive gastritis was most frequent cause.[6]

Laboratory findings when patient first admitted were the platelet count 153,000/μL and hematocryte 39%. Patient was given ringer lactate/4 hours. Hematocryte after 4-hours fluid replacement was

decrease to 38%. There was also thrombocytopenia 134,000/μL, and leukopenia 4,800/μL.

The positive tourniquet test along with thrombocytopenia, leukopenia, and recent fever confirm dengue hemorrhagic fever as the diagnosis. WHO definition for dengue hemorrhagic fever are as follows:[7] (1) Current or recent fever; (2) Platelet count < 100,000/ ìL (3) Hemorrhagic manifestation; (4) Objective evidence of plasma leakage caused by increased vascular permeability manifested by at least one of the following: elevated hematocryte (< 20% over baseline or a similar drop after intravenous replacement); pleural effusion (e.g. ascites); low protein.

Positive tourniquet confirms DF. However, level of thrombocyte at the time of hematemesis was in normal range 153,000/μL. An early diagnosis of DHF is difficult because the WHO clinical and laboratory criteria for DHF may be manifested only in the late phase of acute illness.[8] As in the next day of hospitalization, clinically and laboratorial, patient develop more obvious DF manifestation. Thrombocytes level was lower and patient no longer fever. IgG anti dengue was positive at day 7 (day 10 of illness).

When GI bleeding is suspected, rapid assessment of the patient is carried out to monitor and determine whether the bleeding acute or chronic? Is the patient hemodynamically stable or unstable?. It is helpful to confirm the presence of GI bleeding with inspection of the stool or nasogastric aspirate, but the first goal is to stabilize the patient. Vital signs are recorded, the patient's skin and mucous membranes are inspected for pallor or a sign of shock, and blood is sent to the laboratory for complete blood count, routine chemistries, and clotting studies. Blood for typing and cross matching is sent to the blood bank so that transfusions can be given without delay if needed.[9]

The presence of GI bleeding in this patient was confirmed by both inspection of the stool and nasogastric aspirate. During admitted, patient's was hemodynamically stable.

The hematocryte does not fall immediately with hemorrhage because of proportionate reductions of plasma and red cell volumes (i.e. "people bleed whole blood"). Hence, during this time, the severity of bleeding must not be underestimated because of a normal or only minimally decreased hematocryte. As extra vascular fluid enters the vascular space to restore volume, the hematocryte falls. This process, which begins shortly after the onset of bleeding, is not complete for 24 to 72 hours, by which time the total vascular volume has been restored. At this point, plasma volume is larger than normal and the hematocryte is at its lowest point. This sequence is modified by pre-existing abnormalities in vascular volume or by administration of exogenous fluids and blood.[9]

Patient's hematocryte was 39% (N: 40-48), and 4 hours later 38%. This minimally decrease hematocryte along with subside symptoms of bleeding and stability of patient's hemodynamic status, should not be interpreted as a definite indication of recurrent bleeding. The rapid intravenous replacement of fluid and electrolytes using normal saline can often sustain patients until they have a spontaneous recovery. Colloid preparations, such as dextran 70, should be given if the pulse pressure is 10 mmHg or less or the hematocryte remains elevated after fluid replacement.[10]

On second day of hospitalization, patient complaint passaging of bright red blood from the rectum. The laboratory work-up reveals a more pronounced DHF symptom. The increase of hemoglobin and hematocryte (hemoglobin 15.8 g/dL, hematocryte 43.8%), leukopenia 2,100/μL and thrombocytopenia 64,000/μL.

The diagnosis was grade 2 dengue hemorrhagic fever with hemorrhoid and history of hematemesis. The management was close monitoring on vital signs and administration of fluids.

Nausea and epigastric pain before vomiting and history of herbs he had been taking and alcohol consumption suggested an erosive gastritis as the cause. Other possible diagnosis to be considered was esophageal varices or Mallory Weiss tear. An upper gastrointestinal endoscopy then scheduled to confirm the diagnosis.

Sudden onset of three-day fever with constitutional symptom such as headache, joint and muscular pain with positive tourniquet test due to dengue fever. Classic dengue fever is characterized by the sudden onset of fever and a variety of non specific signs and symptoms, including frontal headache, retro-orbital pain, body aches, nausea, vomiting, joint pains, weakness, and rash.[11,12]

Upper gastrointestinal bleeding occurred in a median of 4 days (range 1-9) after the onset of fever in DHF patient while the most severe thrombocytopenia was reported on day 4-5 after the onset of fever.[1] In this patient the hematemesis appear on day three of febrile, and the lowest platelet count was on day 8.

Raquel et al, revealed that DHF patients had a lower thrombocytes count, had more hemorrhagic manifestation and gastrointestinal manifestation than dengue fever patient. The critical stage of the disease is reached at the end of febrile phase. It is at this time that thrombocytopenia is pronounced which may lead to bleeding.[13]

The pathogenesis of abnormal hemostasis in DHF includes vasculopathy (from anaphylotoxin released by complement activation), thrombopathy (decreased platelet production increase destruction), and

coagulopathy, including prothrombin complex deficiency due to liver damaged and consumptive coagulopathy.[14]

This patient was likely to develop the secondary dengue viral infection. IgG was positive at day 10, while IgM was negative. There should have been a re-evaluation of patient's IgM to confirm a secondary newly infection.

Dengue blot had a sensitivity of 25.9% in detecting primary infection and 100% in detecting secondary infections hence this is suitable for use in areas where majority of cases are secondary infection.[11]

Three to four days following primary infection, IgM appeared and gradually increase to the peak level, then decrease to disappear in 30-60 days. The raise titer of IgM followed by IgG, which increase to the peak level within 15 days and decrease gradually that it stays in small titer for life. In secondary infection, IgM has already disappeared and IgG stays in a small titer. Newly infected by dengue virus for the second time, IgG will be produced in high titer rapidly while IgM followed.[13]

In secondary infections, antibodies are largely of the IgG class and are directed against the antigens of the flavivirus group on the dengue virus complex or subcomplex.[14]

The risk of DHF is higher in patients experiencing a second dengue infection, DHF also occurs in patients who have primary infections, which suggests that heterogonous dengue antibody (previous infection) is not a prerequisite for DHF. Furthermore, some strains of dengue viruses cannot be enhanced in vitro. Both field evidence and laboratory evidence support a more prominent role of viral factors in the pathogenesis of DHF and suggest that virus strain and serotype are also important risk factors for severe disease. Hemorrhage may occur without vascular leakage, suggesting another pathogenetic mechanism.[15]

The endoscopic findings of this patient were mild erosive gastritis. It is consistent with Chiu YC et al. who found hemorrhagic (and/or) erosive gastritis as the most common findings among dengue patients with gastrointestinal bleeding.[1] Tsai CJ et al, found gastric ulcers or duodenal ulcers; superficial and hemorrhagic gastritis as endoscopic feature of DHF patients, and 50% patients had history of peptic ulcer and other 50% were not. So, both DF patient with or without history of peptic ulcer symptom can develop gastrointestinal bleeding.[4]

Patient did admit consumed traditional herbs 2 days before admission and there was a history of alcoholism. The medicine he had been taking during early days of fever also contributes to erosive gastritis. It was confirmed by endoscopic findings, mild erosive gastritis. Patient presented with hematemesis melena because of erosive gastritis, and DHF contributes to it.

Pathology anatomy examination reveals a non-atrophic chronic gastritis. It is probably due to the alcohol that the patient had consumed two years ago.

Evidence of intestinal mucosal injury in patients with dengue infection was demonstrated in a study determine whether there is an association between dengue infection and intestinal mucosal injury. Serum levels of intestinal fatty acid binding protein (I-FABP) were used as a specific marker for mucosal injury. The patients with DHF grade IV had the highest levels of serum I-FABP, ALT, and AST compared to the other groups. However, there were no differences in serum I-FABP, ALT, and AST levels among patients with DF, DHF grade I, grade II, and grade III. Patients with DHF grade IV had high serum I-FABP levels and had associated liver injury.[16]

Perng DS et al, concluded that: 58.5% of the dengue fever patient disclosed hemorrhagic gastritis in their endoscopic findings. Patients with platelet count < 50,000/μL suffered from upper GI bleeding at a detection rate of around 48.6%. On the other hand, the detection rate was around 29.7% in those patients with platelet count over 50,000/μL. Thus a significant difference was shown ($p < 0.025$). The platelet count decreased significantly in patients who had had oral medication before endoscopy compared to those without oral medication. The detection rate of upper GI bleeding was 40.6% and 26% respectively ($p < 0.025$). Most upper GI bleeding cases occurred after the 4th day of onset. There was no significant relationship between upper GI bleeding and symptoms of epigastralgia or cutaneous eruption. In cases of presenting hemorrhagic gastritis and superficial plus hemorrhagic gastritis by endoscopy, the detection rate of upper GI bleeding seemed higher but there was no statistical difference.[17]

DF is an acute disease that may induce severe hemorrhage by multifactor pathogenesis. Mucosal injury, vaculopathy, platelet deficiencies and dysfunction, and blood coagulation defects are some of the proposed mechanism. Erosive gastritis was the most common endoscopy findings in DHF patient. Patient in this case developed chronic gastritis, which became erosive once he suffered from dengue fever.

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