

Dengue Hemorrhagic Fever/Dengue Shock Syndrome in Hereditary Spherocytosis

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Abstract

Background: Dengue Hemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS) occurs only in a small number of dengue fever (DF). This condition, when coupled with a form of congenital hemolytic anemia called Hereditary Spherocytosis (HS), will turn a relatively manageable case of DF into a complicated condition with very poor prognosis.

Case Presentation: Here we report a case of a 19-year-old male student from Manila who came in with fever, jaundice, and dengue warning signs. He was also diagnosed with HS. This compounding infection initiated a hemolytic crisis of his HS, causing severe bleeding and multiple organ failure on top of DHF/DSS. The progression of the disease

started with bleeding, and later on with altered sensorium (encephalopathy), respiratory failure, and ultimately, demise.

Conclusion: DHF/DSS together with HS may cause a hemolytic crisis. High RBC turnover and heightened erythroid marrow activity in HS makes a patient vulnerable to develop aplastic crisis due to dengue virus infection. Erythroid marrow failure may result in profound anemia, heart failure, hypoxia, cardiovascular collapse, and death.

Keywords: Dengue Hemorrhagic Fever/Dengue Shock Syndrome, Hereditary Spherocytosis

Introduction

Hereditary spherocytosis (HS) is one of the common familial hemolytic disorders, with approximately 75% of cases displaying autosomal dominant pattern of inheritance and the remaining cases due to recessive forms and de novo mutations. HS is the clinical consequence of mutations in the genes encoding ankyrin, band 3, alpha spectrin, beta spectrin, RhAG or pallidin. One survey of 166 HS kindreds in Portugal found spectrin or spectrin/ankyrin deficiency in 60%, band 3 deficiency in 23%, isolated pallidin deficiency in 2.0% and no membrane protein abnormalities in the remaining 15%.¹ The morphologic hallmark of this condition is the presence of microspherocytes caused by loss of membrane surface area due to intrinsic genetic defect in spectrin. The triad of anemia, jaundice and splenomegaly is the usual clinical manifestation. Aside from clinical symptoms and typical family history, laboratory exams such as presence of microspherocytes and a positive osmotic fragility test in vitro confirms the diagnosis of HS. Clinical severity is variable with most patients having a well-compensated hemolytic anemia.

Some individuals are asymptomatic, whereas others have severe hemolytic anemia requiring erythrocyte transfusion. Hemolytic crisis is the most common complication.²

Dengue fever (DF) is a rapidly spreading mosquito-borne disease, with *Aedes aegypti* as its principal vector, affecting millions of people worldwide especially in the tropics and subtropics. Currently, there are four known distinct serotypes (DENV 1-4).³ Infection with one serotype is not protective against the others. Sequential infections may lead to dengue hemorrhagic fever (DHF), and sometimes with shock (DSS) mediated by an immune response called antibody-dependent enhancement⁴. After an incubation period of two to seven days, a typical patient experiences sudden onset of fever, headache, retroorbital pain, and back pain along with severe myalgia that gave rise to the colloquial designation "break-bone fever". The illness may last for seven days, and may be accompanied by a maculopapular rash near the time of defervescence. Epistaxis and scattered petechiae are often noted in uncomplicated dengue. However, there may be severe bleeding during subsequent infection. Laboratory findings include leukopenia, thrombocytopenia, and, in many cases, serum aminotransferase elevations³. Hemoconcentration from vascular leakage, which is usually evident, is most marked in DHF/DSS. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, convulsions) are all poor prognostic signs.³ Patients with hematological diseases like idiopathic thrombocytopenic purpura, leukemias

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and transplant recipients are equally vulnerable to dengue⁵.

Case Presentation

A 19-year-old male college student from Manila was admitted due to fever of five days duration with maximum temperature of 38.5°C. This was accompanied by hematemesis, melena, and gross hematuria. He was diagnosed with "anemia" in 2001, but was poorly compliant to iron replacement. He had DF in 2005, and typhoid fever in 2007. His mother claims to have HS, diagnosed by osmotic fragility test. His brother has chronic liver disease and gallstone. He has a nephew who has α -thalassemia, and a maternal grandaunt with aplastic anemia.

He had normal vital signs on admission, and the rest of the physical examination was unremarkable except for icterisia, right upper quadrant tenderness on direct abdominal palpation, and a palpable splenic tip on deep inhalation. Complete blood count (CBC) revealed hemoglobin 135 g/dL, hematocrit 0.35, (MCV 85.70, MCH 32.80, MCHC 38.2, RDW 19.30, MPV 8.20) platelet 200,000/mm³, WBC 6,300/mm³ (neutrophils 59%, lymphocytes 41%). Other work-ups revealed activated partial thromboplastin time (aPTT) 76.5 (normal control 33.7), ALT 141 U/L, AST 924 U/L, and serum creatinine 1.1 mg/dL. Dengue NS1 was positive.

He was admitted as a case of DF with warning signs. Congenital hemolytic anemia probably secondary to HS was also entertained after review of peripheral smear which showed anisocytosis with microspherocytes (Figure 1). He was initially given intravenous fluid replacement. During subsequent hospital days, he had repeated episodes of hematemesis, melena and hematochezia. Despite adequate fluid resuscitation, serial CBC determination revealed progressive drop in hemoglobin (76 g/dL to 54 g/dL), hematocrit (0.19 to 0.14), platelet (105,000/mm³ to 58,000/mm³), and WBC (5,300/mm³ (with 40% neutrophils) to 3,900/mm³ (with 10% neutrophils)). Progressive prolongation of aPTT (92.1 to 100.1) was also observed. He was transfused with the following: two units whole blood, nine units packed RBC, 22 units fresh frozen plasma, and 10 units platelet concentrate. There was deepening of jaundice accompanied by increase in ALT (4,845 U/L). Serum creatinine (4.5 mg/dL) was further elevated as well.

On the third hospital day, he became lethargic, unable to recognize family members, had difficulty following commands and with behavioral changes. Plain cranial CT scan showed small hypodense foci in the posterior limbic and left lentiform capsule, and possible lacunar infarct with no hemorrhage. The encephalopathy was attributed to the acute hepatic failure and the hypoxemia. He had endotracheal

intubation due to impending respiratory failure. Despite hydration and blood transfusion, he had persistent bleeding and hypotension. He then went into cardiorespiratory arrest and relatives signed do not resuscitate status. Post-mortem examination was offered but was refused by the family.

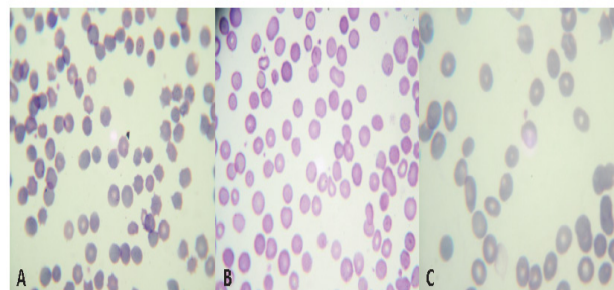


Figure 1: Peripheral blood smear of patient (A), the patient's brother (B) and the patient's mother (C), all showing anisocytosis and presence of microspherocytes.

Peripheral smears from both the mother and the brother were examined, all showing anisocytosis with microspherocytes, compatible with HS (Figure 1). Osmotic fragility testing was done to one of his brothers which also showed a positive result.

Discussion

There has not been a reported case of DF or DHF/DSS in a patient with HS according to *PubMed*, *Cochrane* and other database. DHF/DSS occurs only in a very few cases of DF.³

DHF/DSS is characterized by rapid onset of capillary leakage accompanied by thrombocytopenia, altered hemostasis, and damage to the liver.^{9,10} It generally occurs in secondary infection of another serotype.¹¹ Previous infection with any of the four dengue-virus serotypes may result in the production of non-protective antiviral antibodies that bind to the surface of the new infecting dengue-virus serotype. The previously formed antiviral antibodies interact with the Fc receptor of the dengue virus. This results in an accelerated rate of internalization and cell infection by immune-complexes during a secondary infection—a mechanism termed as antibody-dependent enhancement, characterized by higher viremia and more severe clinical manifestations^{4,12,13}. The immune complexes lead to activation of the classic complement pathway. Cross-reactivity at the T cell level results in the release of cytokines like interferon γ and tumor necrosis factor α .⁴ Of the four dengue-virus serotypes, serotype 2 exhibits comparatively more severe clinical manifestations^{11,14}.

Liver damage in dengue virus infection is due to viral replication in hepatocytes, cytokine-related

damage, and partly due to ischemic hepatitis, which can lead to severe coagulopathy, encephalopathy and acidosis^{15,16}. Elevations in serum AST appear to be greater than ALT levels¹⁷. Mortality associated with fulminant hepatitis is higher in those with circulatory failure, severe thrombocytopenia and spontaneous bleeding. Death in these cases occur in the first week of hospitalization, with fatality rate as high as 12-44%^{18,19,20}. There is no specific therapy for fulminant hepatitis in dengue. Cytokines as cause of endothelial and vascular permeability and in uremic patient, endothelial damage may contribute to DHS/DSS pathogenesis²¹.

Congenital hemolytic anemia was also entertained in this patient because of the following points: history of chronic anemia, splenomegaly by physical examination, family history of chronic anemia, sibling with development of gallstones at an early age despite having a normal hemoglobin level on admission. The apparent normal hemoglobin level may be secondary to the hemoconcentration in an otherwise chronic anemia patient. Review of the peripheral smear of the patient, the brother, and the mother showed anisopoikilocytosis with numerous microspherocytes. Due to the critical status of the patient, osmotic fragility test was done to the sibling and results confirmed hereditary spherocytosis. HS is due to abnormalities in cell membrane protein called spectrin²². The deficiency of this protein, which is involved in the attachment of the cytoskeleton to the membrane integral domain, results in a loss of surface area and leads to spheroid, osmotically fragile cells that are selectively trapped in the spleen^{1,2}. The osmotic fragility test was done to one of our patient's brother to confirm the diagnosis of HS, since it is a familial disorder. During the test, the patient's red blood cells were placed in different concentrations of saline solution for 24 hours. When normal red blood cells are placed in hypertonic solution, they absorb water until the cell membrane bursts. In contrast, spherocytes do not tolerate weak saline solutions, causing them to burst sooner than normal cells, as what have happened in our case.

Symptoms of HS vary depending on the severity of the disease. Most patients have only mild anemia, and generally live a normal life without restrictions in physical activity similar to our patient. Thus, most of them remain undiagnosed for years or decades if hemolysis is only mild. These patients compensate by making more red blood cells, which is measured by the reticulocyte (immature red blood cell) count. However, infection, fever and stress can stimulate the spleen to destroy more red blood cells than usual. This is primarily due to the abnormal shape of the spherocytes, wherein they are rapidly culled from the circulation, resulting in extravascular hemolysis. If

this occurs, hemoglobin level drops and the bilirubin level may increase, causing pallor and jaundice. Moreover, infection, usually viral, can cause the bone marrow to stop cell production temporarily. This is called an aplastic crisis. A hemolytic crisis occurs when more red blood cells are hemolyzed than can be replaced. A moderate, self-limiting anemia then develops.

In HS, due to the abnormal shape of the spherocytes, the red blood cells are rapidly culled from the circulation by the spleen, resulting in extravascular hemolysis. Therefore, in our patient with both conditions, there is accelerated loss of blood despite adequate blood component therapy replacement. The bleeding was further compounded by acute hepatic failure contributing to coagulopathy. Standard management of DHF/DSS was not enough to control the disease progression, even if aggressive measures were given.

Our patient expired due to DHF/DSS. He had all poor prognostic factors present including shock, multifocal bleeding, and CNS involvement (encephalopathy). To add injury, the patient developed acute hepatic failure, and was diagnosed to have a chronic hematologic problem. Thus, despite the multitude of efforts done, the many units of blood and blood products transfused, it was not enough to replenish the losses, to contain the disease and the rapid multi-organ damage was not prevented.

DHF/DSS is a dangerous complication of dengue infection and is associated with high mortality. This condition together with HS can cause a hemolytic crisis. High RBC turnover and heightened erythroid marrow activity in HS make patient vulnerable to develop aplastic crisis due to dengue virus infection. Erythroid marrow failure may result in profound anemia, heart failure, hypoxia, cardiovascular collapse, and death.

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