Dengue Virus-associated Hemophagocytic Syndrome and Dyserythropoiesis: A Case Report

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A 33-year-old man had dengue hemorrhagic fever with initial presentation of fever, leukocytosis, and thrombocytopenia. The cause of the subsequent rapid decline in red cell counts without evidence of intravascular hemolysis or massive bleeding was confirmed as hemophagocytosis and dyserythropoiesis by bone marrow study. The patient recovered with supportive care and the bone marrow pattern was normal on repeated bone marrow study. To our knowledge, this is the first reported case of dengue virus-associated hemophagocytosis and dyserythropoiesis in Taiwan. Clinicians should consider that the occurrence of hemophagocytosis and dyserythropoiesis could be due to dengue virus infection. That this dengue virus infection was confirmed by a positive serology result at the convalescent stage but not at the acute symptomatic stage underlines the need for a second dengue serology study, as dengue infection can be missed due to an initial negative serology result.

Key Words: hemophagocytosis, dengue fever
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Dengue fever caused by dengue virus is an important mosquito-transmitted disease due to its increased worldwide incidence and its related complications [1]. The most common manifestations of dengue virus infection are self-limiting high fever and musculoskeletal pain. Some cases may present with severe bleeding or even shock that is classified as dengue hemorrhagic fever (DHF) [1].

Early neutropenia, with subsequent lymphocytosis and a decrease in platelet count, and markedly hypocellular marrow with abnormal megakaryocytopoiesis in the early stage are common hematologic presentations of dengue infection [2]. Several observations have been made on changes in the bone marrow of patients with dengue fever and DHF [2–16]. However, there are few reports with detailed studies of marrow aspirates throughout the course of the disease [6].

Hemophagocytosis is an uncommon presentation of dengue infection. The cause of the exceptional hematopoietic response of some patients to viral infections remains obscure, but this response raises the distinct possibility of host factors of which we are not aware [2]. We describe a patient with DHF who developed hemophagocytosis and dyserythropoiesis and recovered. We also review previously reported bone marrow findings during dengue infection.

Case Presentation

A 33-year-old Chinese male patient had had fever and chills associated with general muscle soreness, headache, and lower back pain since November 6, 2002. He came to the emergency room of our medical center on November 10, 2002 because his fever did not subside after primary management. He also had abdominal pain, poor appetite, and diarrhea for 2 days. Physical examination revealed petechiae over both lower legs and splenomegaly.

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Laboratory examination on admission showed a white blood cell (WBC) count of 24,820/mm^3, red blood cell (RBC) count of 5,580,000/mm^3, hemoglobin of 18.2 g/dL, hematocrit of 53.0%, and platelet count of 4,000/mm^3. Differential leukocyte count showed a predominance of polymorphonuclear cells (segmented, 67%; band, 8%; lymphocytes, 8%; monocytes, 15%; normoblasts, 1%). The aspartate transaminase concentration was 179 U/L, alanine transaminase concentration was 88 U/L, blood urea nitrogen was 22 mg/dL, creatinine concentration was 1.0 mg/dL, glucose concentration was 115 mg/dL, C-reactive protein level was 0.4 μg/mL, prothrombin time (PT) was 12/10.9 seconds (case/control), activated partial thromboplastin time (APTT) was 50.3/30.4 seconds (case/control), haptoglobulin concentration was less than 5.83 mg/dL (normal, 13–163 mg/dL), Coombs' test (direct and indirect) was negative, and lactate dehydrogenase level was 1,243 U/L (normal, 180–460 U/L). The stool occult blood test result was 4+.

At 2 days after admission, WBC count had decreased to 16,890/mm^3, hemoglobin level to 12.0 g/dL, hematocrit to 35.8%, and platelet count to 1,600/mm^3. Over a 6-day period (November 10–15), the WBC count dropped to 5,160/mm^3, the RBC count to 4,020,000/mm^3, and the hemoglobin to 12.4 g/dL. Routine urine tests on the 6th day revealed no pyuria and no hematuria, but dipstick tests were positive for bilirubin (1+) and urine protein (1+). The reticulocyte index was 0.45%. The patient had a positive result for hepatitis B surface antigen and a negative result for hepatitis C antibody. Tests for heterophil antibody and cytomegalovirus immunoglobulin (Ig) M were negative, while that for Epstein-Barr virus nucleus antigen antibody was positive. Antinuclear antibody was absent. Blood culture on admission was negative for bacteria. Abdominal sonography 7 days after admission showed bilateral pleural effusion, ascites, splenomegaly, gall bladder sludge, and gall bladder wall thickening. Chest roentgenography revealed bilateral lower lung pleural effusion.

Bone marrow was examined on the 9th day after fever because of marked leukocytosis and the rapid decrease in hemoglobin and platelet count. Marrow aspiration showed normal cellularity (50%) with adequate megakaryocytes and normal myeloid differentiation. However, dyserythropoiesis syndrome (nucleus budding, multiple nuclei, and some megaloblastic change) and hemophagocytosis were found (Figure 1).

The patient received supportive care without antimicrobial therapy. His fever subsided on the 10th day after symptoms appeared. He was discharged on the 10th hospi-

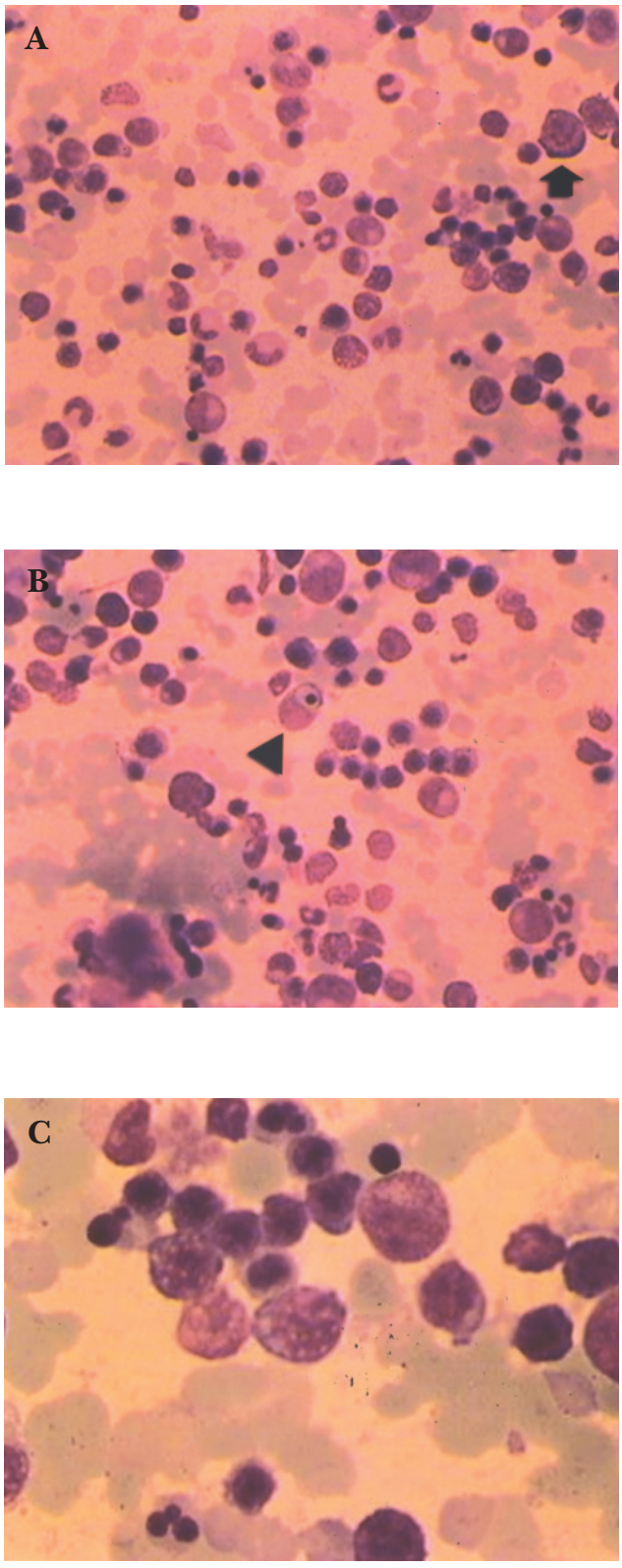

Figure 1. *Initial bone marrow examination shows: (A) normal cellularity with erythroid hyperplasia and megaloblastoid erythropoiesis (arrow); (B) hemophagocytosis (arrowhead). (C) The nuclear budding and multinucleation characteristics of dyserythropoiesis are clearly seen under high-power magnification (× 1,000).*

talization day when the fever had subsided and the WBC count was 4,760/mm^3, hemoglobin was 12 g/dL, and platelet count was 77,000/mm^3. Dengue virus serology by enzyme-linked immunosorbent assay, performed by The Center for Disease Control, Taiwan, 6 days after onset of fever and symptoms, was negative for IgG and IgM antibodies to dengue virus [17]. Convalescent serology tests on November 23 and December 20 were positive for IgG and IgM antibodies to dengue virus, confirming the dengue virus infection. According to his clinical manifestations, the patient was diagnosed as having DHF: his diagnostic criteria were acute febrile illness, bleeding symptoms or signs, thrombocytopenia (< 10^5 cells/μL), and evidence of plasma leakage (pleural effusion, ascites) [1].

Follow-up examination 1 month later showed no sequelae. The laboratory data were as follows: WBC, 9,820/mm^3; hemoglobin, 13.6 g/dL; hematocrit, 43.4%; platelet count, 266,000/mm^3; PT, 11.5/12.1 seconds; and APTT, 31.8/29.8 seconds. Repeated bone marrow aspiration showed recovery to a normal marrow pattern and disappearance of dyserythropoiesis (Figure 2).

Discussion

Infection with dengue virus commonly produces neutropenia with lymphocytosis and thrombocytopenia [18]. Hematocrit, hemoglobin, PT, and APTT are normal in uncomplicated classical dengue fever, but they may alter in dengue fever complicated with severe hemorrhage [19].

Our case lacked the characteristic leukopenia of adult dengue. Leukopenia (< 5,000/mm^3) is found in most non-shock cases of dengue infection [7]. Only 16% of mild cases have leukocytosis, which appears during the recovery stage, whereas 67% of shock cases and 66% of mortality cases have pronounced leukocytosis [20]. Clinically, leukocytosis is an ominous sign for dengue infection [20]; our DHF case had this hematologic finding.

The longer survival of erythrocytes compared with platelets and granulocytes makes the hematocrit relatively insensitive to modest or temporary changes in either RBC production or survival [21]. There was no clinical evidence of intravascular hemolysis and no massive bleeding clinically in our case; bone marrow aspiration showed that the sudden and significant fall in RBC counts resulted from intramedullary destruction of blood cells by hemophagocytic histiocytes.

Bone marrow aspiration is not a usual procedure for dengue infection cases, mostly due to the risk of bleeding and because most patients have classic dengue fever, where changes in blood cell counts recover.

Thrombocytopenia is often seen among dengue-infected patients. Hemophagocytosis is regarded as one of the causes of thrombocytopenia [9,22]. Other processes that interfere with platelet cells, acting successively or in combination, are: early transient marrow suppression with damage to megakaryocytes [23]; platelet aggregation with endothelial cells targeted by dengue viruses [24]; and immune destruction of platelets, with dengue antibody complexes found on membranes [25].

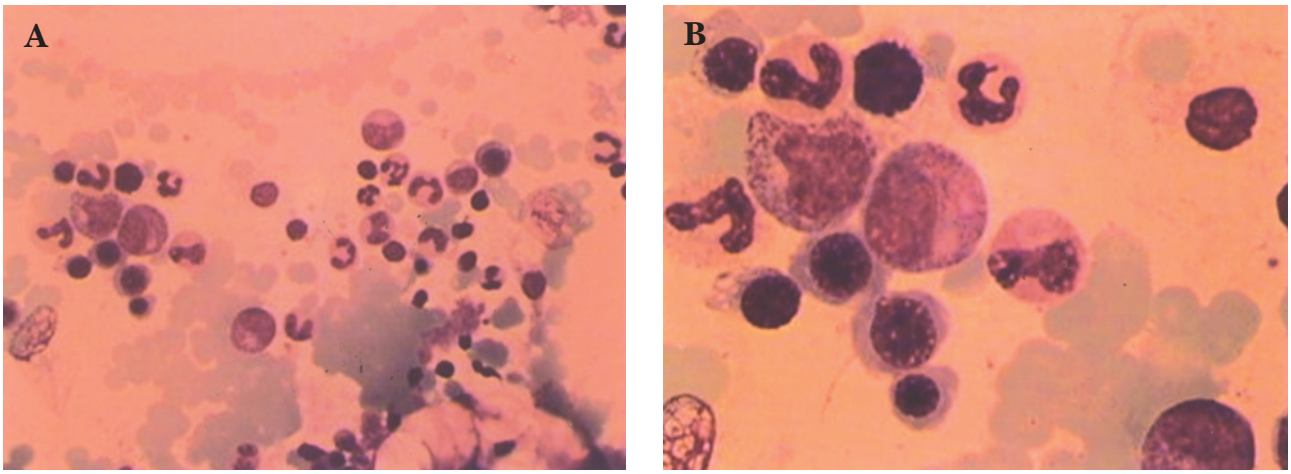

Figure 2. *Bone marrow examination at follow-up: (A) nearly normal marrow with a myeloid:erythroid ratio of 3.5:1 (× 400); (B) disappearance of the dyserythropoiesis (× 1,000).*

In dengue-infected patients, bone marrow hypoplasia is typical [2]. Dengue infection of hematopoietic cells is not cytotoxic but slows cell proliferation [26]. Erythroid progenitor colonies from dengue-infected cultures are smaller and abnormally dispersed [26,27]. Dyserythropoiesis shows as erythroid hyperplasia with arrest of maturation [5].

Dengue-related hemophagocytosis has been described in the literature [6,9–13]. The self-limiting hemophagocytosis syndrome with supportive care in our case follows a similar disease process to other surviving dengue-associated hemophagocytosis cases [21–23] and most reactive hemophagocytosis cases [28]. However, most reported cases of hemophagocytic syndrome are DHF cases and from postmortem bone marrow study [6,14,22,24]. Nelson et al proposed that hemophagocytosis was present in the terminal stage of dengue infection because seven postmortem cases and two severe cases (one with prolonged shock and one with severe epistaxis) had variable levels of hemophagocytosis [6], while no hemophagocytosis was found in another 22 bone marrow samples from dengue fever cases [7]. In contrast, two postmortem bone marrow studies in 12 and 100 DHF cases, respectively, did not find features of hemophagocytosis [14,15]. A causal relationship between hemophagocytosis and the severity of dengue infection has been suggested [6] but not fully established. Other studies on bone marrow in dengue-infected cases did not find hemophagocytosis, which shows that hemophagocytosis is not a common presentation of dengue infection [5,2,16].

The initially negative dengue serology result and the concurrent bone marrow finding of hemophagocytosis and dyserythropoiesis might lead to a diagnosis of myelodysplastic syndrome or hemophagocytosis, including malignant histiocytosis, which may require a different treatment. Our case had reactive hemophagocytosis, which may occur during dengue infection, and confirmed reversible bone marrow changes after infection. Clinicians should consider the possibility that hemophagocytosis could be a complication of dengue infection, which requires bone marrow aspiration and second serology study for dengue virus at the recovery stage.

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登革熱病毒相關之嗜血症候群及紅血球生成不良 — 病例報告

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一位以發燒、白血球增多、血小板低下為初期表徵之33歲男性登革出血熱患者，在沒有大量出血及血管內溶血的情況下其紅血球數目急速下降，經骨髓檢查證實為嗜血症候群及紅血球生成不良。病人病情在支持性治療下恢復，覆檢骨髓檢查也顯示恢復為正常骨髓。這台灣首次報告的登革熱病毒相關之嗜血症候群及紅血球生成不良提供臨床醫師了解嗜血症候群可能和登革熱病毒有關，而此病人在急性症狀期之登革熱血清學檢查為陰性，在疾病恢復期登革熱血清學檢查才呈陽性之情形也可提醒在只做急性期登革熱血清學檢查的情況下可能會誤失登革熱感染之診斷。

關鍵詞：嗜血症候群，登革熱

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