

Irreversible Aplastic Anemia secondary to Dengue Fever, Case report and review of literature

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Abstract: Aplastic anemia is a syndrome of bone marrow failure characterized by complete or partial disappearance of hematopoietic tissue without abnormal cellular proliferation. This is a rare complication of infections, such as dengue hemorrhagic fever and other arboviruses. Dengue fever has rarely been reported as an etiology for aplastic anemia. A 55 years old male patient presented with severe persistent pancytopenia and transfusions dependence for one year after infection with dengue hemorrhagic fever, diagnosis was confirmed as aplastic anemia, Our late management with corticosteroids, Gamma Globulins, and cyclosporine were ineffective, the only remaining option after that longstanding complication was Allogenic bone marrow transplantation which managed to induce complete remission. Dengue virus induced aplastic anemia is a rare entity, but it must be immediately identified for better outcome. Immunosuppressive therapy can induce remission if given early at the course of illness and spares the need for HLA matched bone marrow transplant.

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Key words: *Aplastic Anemia, Dengue Fever, immunosuppressive therapy.*

Introduction:

Dengue fever is a painful, debilitating mosquito-borne disease caused by any one of four closely related dengue viruses. These viruses are related to the viruses that cause West Nile infection and yellow fever. The global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk. Severe dengue is a leading cause of serious illness and death especially among children in some Asian and Latin American countries. Severe dengue is a potentially deadly complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment, in this study, we are focusing in another well identified complication of Dengue Fever in the form of severe irreversible aplastic anemia that can respond to immune suppressive medications if identified early at the course of the disease and sparing the need for bone marrow transplant in case of delayed management.

Case Report:

A 55 years old Sudanese male was admitted to emergency department of King Abdul Aziz Hospital "Jeddah" complaining of exertional dyspnea and generalized weakness of one year duration that progressed during the last six months to be on mild

exertion then at rest. One year prior to this admission the patient experienced fever, myalgia, Petechiae over the extremities and diagnosis was confirmed as dengue hemorrhagic fever by serology and PCR at a local hospital where he received only symptomatic treatment for the fever, nausea and myalgia. There was Persistent Pancytopenia during that admission despite repeated platelets and whole blood transfusions and patient was discharged after 2 weeks with moderate Pancytopenia to be followed up at outpatient hematology clinic, no steroids, immunosuppressive, or any bone marrow stimulant had been administered during the acute infection period. Later on, the patient had intermittent admissions at ER of different hospitals where he also received several transfusions and discharged with partial improvement ranging from mild to moderate Pancytopenia. The patient denied any history of any other medical illness or drug abuse or exposure to possible toxic agent or radiation and no family history of similar condition. The patient resides at an area where dengue fever is endemic but developed the symptoms of acute infection of dengue fever only once. On physical examination patient was conscious, oriented, pale and hemodynamically stable with Temperature 37°C, pulse 105/min regular, blood pressure 119/64, respiratory rate 24/min and SPO2

100% in room air. Laboratory tests at admission showed hemoglobin 3.31 g/dL. Haematocrit 8.7, WBCs 0.8×10^9 (lymphocyte 90.6, neutrophil 4.86), and platelet 13×10^3 , Reticulocytic count was 1.33, MCV 96, MCH 29, MCHC 36.9 (blood film showed normocytic normochromic anemia). Dengue serology was positive for IgG only denoting old infection. Screening for other viruses like cytomegalovirus, Epstein Barr Virus, Parvovirus 19, Hepatitis B and C were negative. Sputum AFB was also negative. Vitamin B12 level 721.7pg/ml, folic acid level 20ng/ml ruling out possibility of megaloblastic anemia. LDH level, Liver enzymes, liver functions, and autoimmune screening were also normal. Bone marrow aspiration and biopsy were eventually done and confirmed the diagnosis of severe aplastic anemia (Fig.1). Specimen revealed scanty particulates of hypocellular neuroaspirate with few myeloblasts, trephine showed picture of Aplastic anemia. Patient received replacement therapy in the form of several transfusions of packed red cells and platelet transfusions, vitamin B12 and folic acid, and antibiotics to cover infection. Regarding the long history (around one year) of irreversible Aplastic anemia despite several admissions and blood transfusions, Allogenic Bone marrow transplant was urged for the patient after failure of last trial with steroids, intravenous Immunoglobulins (IVIG) plus folic acid, iron, and vitamin B₁₂ over 10 days in the last admission. Unfortunately, Chances for transplant rejection are much higher in such a patient who received several blood and blood products transfusions throughout one year of his illness before establishing the diagnosis of irreversible Aplastic anemia secondary to Dengue fever.

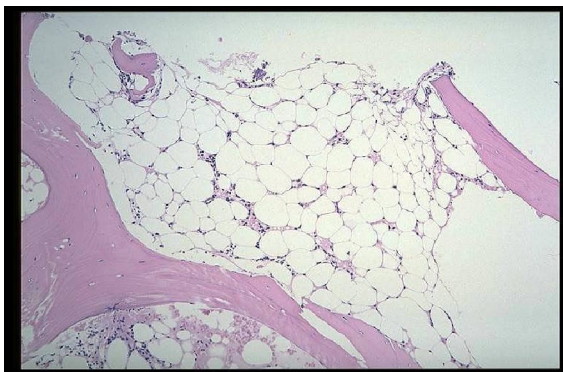


Figure 1: Bone marrow biopsy showing features of severe aplastic anemia.

Discussion:

Aplastic anemia is a syndrome of bone marrow failure characterized by peripheral Pancytopenia and bone marrow hypoplasia. Its annual incidence is about 1.4-3.7 cases per million people.(1) Acquired aplastic

anemia can be idiopathic or from different infectious agents, parvovirus 19, and viral hepatitis (3), drugs (chloramphenicol, antiepileptic, gold salts, antithyroid drugs) toxins and radiations can be identified as a trigger to disease.(2) Viral infections are frequently associated with a transient reduction in the number of circulating blood cells as a consequence of bone marrow suppression. The clinical picture includes an anemia-related syndrome, fever and hemorrhage. Neutropenia and thrombocytopenia are common in dengue infection, and bone marrow is markedly hypocellular, with abnormal megakaryopoiesis.(4) It is known that dengue subtype DEN-4 can reproduce in progenitor cells from the bone marrow.(5) Abnormal vacuolization of lymphocytes appears on the seventh day after viral infection. Reticulocytopenia, lymphocytopenia, thrombocytopenia and granulocytopenia appear in this order.(6) The main differential diagnosis for secondary aplastic anemia includes paroxysmal nocturnal hemoglobinuria, megaloblastic anemia, acute leukemia, myelodysplastic syndrome and viral hemorrhagic fevers. An estimated 390 million dengue infections occur worldwide each year, with about 96 million resulting in illness. Most cases occur in tropical areas of the world, with the greatest risk occurring in: The Indian subcontinent, Central and South America, Western Region in KSA.(7) A rare association between dengue fever and Aplastic anemia has been reported in the medical literature (8, 9, 10, 11) Viruses can infect human hemopoietic cells and alter their proliferative capacity. Clinically the early phase of dengue is dominated by viremia associated marrow failure with poorly characterized immune response. Dengue can induce aplastic anemia through direct bone marrow invasion. Bone marrow may be a major site of virus replication during clinical infection.(12) Our reported patient had developed systemic symptoms of Pancytopenia around the seventh day of the onset of dengue fever infection denoting: dense invasion of the bone marrow by heavy load of the virus, infection by the most virulent serotype DENV4 (2), or secondary infection with dengue virus where the primary infection might pass without diagnosis due to milder symptoms and lack of investigations. No study had managed to identify the exact factors contributing to severe bone marrow suppression in Dengue Fever, But recurrent infection with either the same serotype or different serotype is well established cause of severer bone marrow suppression and hence the chance to development of irreversible aplastic anemia (3). The pathophysiology of dengue-induced aplastic anemia is poorly understood, dengue virus antigen incites an immune response, T lymphocyte activation and γ interferon production and direct viral injury to bone marrow.(12) Other possible causes

could be megaloblastic anemia and myelodysplasia. The levels of vitamin B12 and folic acid were normal in our case report as well as in the few reported patients with the same condition (8, 9, 10) which makes the diagnosis of megaloblastic anemia as a contributing etiology less likely. Myelodysplasia can be excluded, because of the patient age and no history of chemotherapy or radiotherapy, which could lead to myelodysplasia, however, further bone marrow assessment was performed to rule out myelodysplasia and paroxysmal nocturnal hemoglobinuria by karyotyping and flowcytometry studies respectively. (12) Severe manifestations of Dengue fever like aplastic anemia are more prevalent and more fatal on recurrent infection; Dengue antigens induce proliferative responses of PBMC from dengue antibody-positive donors, but do not induce specific proliferative responses of PBMC from dengue antibody-negative donors. IFN gamma is detected in the culture fluids of dengue-immune PBMC stimulated with dengue antigens. The cells that proliferate in the dengue antigen-stimulated bulk cultures have CD3+, CD4+, CD8-, CD16-, and CD20-phenotypes.(14)Studies on Dengue-specific T cell lines were established by using limiting dilution techniques.(15) They have CD3+, CD4+, and CD8-phenotypes, and produce IFN gamma in response to dengue antigens.(14) Culture fluids from dengue-immune PBMC stimulated with dengue antigens, which contain IFN gamma, augment dengue virus infection of human monocytes by dengue virus-antibody complexes. These pathological findings indicate that PBMC from dengue-immune donors contain CD4+ T cells that proliferate and produce IFN gamma after stimulation with dengue antigens, and suggest that the IFN gamma that is produced by these stimulated dengue-specific T cells may contribute to the pathogenesis of dengue hemorrhagic fever and dengue shock syndrome by increasing the number of dengue virus-infected monocytes in the presence of cross-reactive anti-dengue antibodies. (15) Those immunopathological findings may explain the severity of bone marrow suppression and high fatality of dengue infection in case of recurrence.(14) and hence, in endemic areas with the virus patients are more prone to recurrent infection with severer forms of bone marrow supersession. Distinguishing primary from recurrent infection is not always easy since it relies mainly on the medical history, IgG and IgM serology which can be misleading in some patients. Patients with acquired aplastic anemia can be successfully treated with either immunosuppressive therapy or bone marrow transplant. Immunosuppressive therapy is first line of treatment, however for those who do not respond, bone marrow transplant from HLA-matched donor may be offered. It

has been observed that majority of patients respond to this treatment and a high percentage undergoes complete remission. (13)

Conclusion:

Infection with dengue virus can induce aplastic anemia by direct bone marrow invasion. This rare complication must be identified early, since treatment by Immunosuppressive therapy, antithymocytic immunoglobulin, and corticosteroids leading to complete remission can be achieved contrary to delayed diagnosis and management. This case should always remind the physicians to bear in mind the risk of aplastic anemia induced by Dengue fever as the third most serious complication after hemorrhage and Dengue shock syndrome.

References:

1. Yang C, Zhang X. Incidence survey of aplastic anemia in China. *Chin Med Sci J* 1991; 6:203e7.
2. Young N, Mortimer P. Viruses and bone marrow failure. *Blood* 1984; 63:729e37.
3. Kurtzman G, Young N. Viruses and bone marrow failure. *Baillière's Clinical Hematology* 1989; 2(1): 51–67.
4. Bierman HR, Nelson ER. Hemato-depressive virus disease of Thailand. *Ann Intern Med* 1965; 62:867e84.
5. Nakao S, Lai CJ, Young NS. Dengue virus, a Flavivirus, propagates in human bone marrow progenitors and hematopoietic cell lines. *Blood* 1989; 74:1235e40.
6. Young NS. Flaviviruses and bone marrow failure. *JAMA* 1990; 263:3065e8.
7. Centers for Disease Control and Prevention (2010). Locally acquired dengue-Key West, Florida, 2009-2 010. *MMWR*, 59(19): 577-58.
8. Polianna L.M, Geraldo B, Saulo S, Herivaldo F. Dengue and aplastic anemia – A rare association. *Travel Medicine and infectious Disease* 2009;7(2): 118.
9. Bushra Anwar, Khalid Hassan, Ngami Asif, Roshan Parveen Aplastic Anemia Associated with Dengue Fever *Journal of Islamabad Medical & Dental College (JIMDC)*;2012(2):97-98.
10. Khoj L, Baksh R, Aslam M, Kelta M, Albeirouti B, *et al.* (2013) A Case of Dengue Fever-Induced Severe Aplastic Anemia Salvaged by Allogenic Bone Marrow Transplant. *J Leuk (Los Angel)* :120 doi:10.4172/2329-6917.1000120.
11. Mohammed Ramzan,Saty antithymocytic immunoglobulin a Prakash, Yadav, Anupam Sachdeva Post-dengue fever severe aplastic anemia :a rare association *Hematol Oncol Stem Cell Ther* 2012;5(2):122-124.
12. Kurane I, Innis BL, Nisalak A, Hoke C,

- Nimmannitya S, Meager A, Ennis FA: Human T cell responses to dengue virus antigens. Proliferative responses and interferon gamma production. *J Clin Invest* 1989; 83:506. Ullah K, Satti TM, Ahmed P, *et al.* Successful Allogenic stem cells transplantation in severe Aplastic anemia complicated by dengue Fever. *J Coll Physicians Surg Pak*. 2007; 17(10):635- 6.
13. Jessie K., Fong M. Y., Devi S., Lam S. K., Wong K. T. Localization of dengue virus in naturally infected human tissues, by immunohistochemistry and in situ hybridization. *Journal of Infectious* 10.1086/383043.
 14. Rothman A. L., Ennis F. A. Immunopathogenesis of dengue hemorrhagic fever. *Virology*. 1999; 257(1):1–6. Doi: 10.1006/viro.1999.9656.
 15. Braga E. L. A., Moura P., Pinto L. M. O., Ignácio S. R. N., Oliveira M. J. C., Cordeiro M. T., Kubelka C. F. Detection of circulant tumor necrosis factor- α , soluble tumor necrosis factor p75 and interferon- γ in Brazilian patients with dengue fever and dengue hemorrhagic fever. *Memorias do Instituto Oswaldo Cruz*. 2001;96(2):229–232.

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