Case Report

Agranulocytosis in Dengue Hemorrhagic Fever: A Neglected Condition

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A granulocytosis in dengue hemorrhagic fever has not been mentioned, it may probably be included under the term of leucopenia. Here is the case of a 14-year Thai boy presenting with fever and diarrhea for 3 days. He was diagnosed as dengue hemorrhagic fever, grade I because he had hemoconcentration, thrombocytopenia without bleeding and positive IgM dengue antibody. On the 5th day, he developed agranulocytosis and was treated with G-CSF and empirical antibiotics. His leucocyte count was successfully normalized within 1 day and persistently sustained until discharge.

Keywords: *Agranulocytosis, Dengue Hemorrhagic Fever*

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Dengue hemorrhagic fever is an acute febrile illness caused by a mosquito-born virus. Its typical manifestations comprise 3 stages, firstly acute fever and malaise for a few days, followed by a toxic stage which consists of defervescence, hemoconcentration and thrombocytopenia and finally convalescent stage. For white blood cell, leucopenia, neutropenia with increased atypical lymphocyte is commonly found[1,2] but severe neutropenia or agranulocytosis *i.e.* absolute neutrophil less than 500/mm^3[3] which is always resulted from drugs, has never been mentioned. Here was one case of agranulocytosis that is concurrently found in dengue hemorrhagic fever.

Case Report

A Thai male boy, 14-years of age, developed acute and highly sustained fever with malaise for 3 days. During this period, he had abdominal discomfort and watery diarrhea. On physical examination, BT 39.4 Deg Celsius, BP 122/64 mmHg, PR 75/min, he had no dehydration, no hepatosplenomegaly, no rash. His serial CBC are shown in the table, other laboratory results included creatinine 0.8 mg%, hemoculture no growth, AST 97, ALT 35 Na 136.5 K 3.94, dengue rapid test on D3 IgM neg, IgG neg, and on D6 IgM pos IgG neg, stool C/S *E. coli* sense to amikacin, stool examination no RBC no WBC, no parasite, negative occult blood. On D5, he developed severe neutropenia (absolute neutrophil less than 500/mm^3), clindamycin and amikacin were started. Granulocyte colony stimulating factor (G-CSF or Filgrastim or Neupogen®) 300 microgram was also administered subcutaneously. His white blood cell was normalized within 1 day and lasted long until discharge. On D7, he extensively developed macular rash with pruritus over the trunk and extremities therefore antihistamine was prescribed. During the course of the illness, he had fatigue, malaise and poor appetite, parenteral fluid was administered and adjusted to overcome his hemoconcentration. He felt well with good appetite while his fever disappeared on D9.

The serial CBC were shown in the Table 1.

Discussion

The diagnosis of dengue hemorrhagic fever in this case depended on the combination of acute fever for a few days, hemoconcentration, thrombocytopenia and positive dengue IgM antibody[4,5]. It was presumed to be primary infection because IgM turned from negative on D3 to be positive on D6. The clinical course was classical for dengue even the febrile and recovery stages were rather delayed.

For white blood cell change, dengue fever always produces leucopenia, neutropenia, relative lymphocytosis and increased atypical lymphocyte[6].

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Table 1. Showed his serial complete blood count and immunologic status

Day	Hct	WBC	plt	N	L	M	AL	IgM	IgG
3	43.1	2,300	129,000	75	22	0	0	neg	neg
4	41.8	1,500	129,000	46	49	3	2		
5	42.4	1,200	110,000	48	49	0	3		
5	42.2	900	104,000	43	48	1	8		
6	44.9	9,200	104,000	85	14	0	1		
6	42.6	12,900	58,000	94	4	1	1	pos	neg
7	44.1	11,100	57,000	87	13				
8	46.0		67,000						
9	45.2	7,000	170,000						
10	44.2	4,800	243,000	29	45	16	7		

7 serial hematocrit every 6 hours 51.8, 48.0, 45.5
AL: atypical lymphocyte

Severe neutropenia or agranulocytosis (absolute neutrophil count <500/mm^3) has never been mentioned, probably it might be overlooked or unrecognized or neglected under the term of leucopenia[7]. In almost all cases of agranulocytosis, they have been found as drugs side effect. However it can also be found in viral infections such as cytomegalovirus, parvovirus B19[8], Epstein-Barr virus, hepatitis B virus, influenza[9] and HIV[10,11]. In the presented case, agranulocytosis was found on D5 whereas thrombocytopenia was slightly decreased and the latter was more prominent on D6 through D8. Hemoconcentration which was one of the risk factors was obvious on D7. Because he did not take any prior medication, agranulocytosis was presumed to be associated with dengue hemorrhagic fever. However, the patient did not manifest any sign of profound shock. Therefore, agranulocytosis in dengue hemorrhagic fever might not signify the poor prognosis.

Emphasizing on prognosis, leucocytosis had more association with severity than leucopenia[12]. In the presented patient, agranulocytosis happened while the platelet level was slightly decreased and when the latter was progressively lowered, the leukocyte became normal. According to WHO criteria, his clinical severity conformed with dengue hemorrhagic fever, grade I because he had hemoconcentartion and thrombocytopenia without bleeding manifestation[13].

Because of his vulnerability to bacterial sepsis, especially *E. coli*, which he passed with watery stool, he was treated with empirical antibiotics like clindamycin and amikacin even though he had no symptoms denoting agranulocytosis such as sore throat[14].

Without definite guideline for agranulocytosis found in dengue fever, he was treated with granulocyte colony stimulating factor(G-CSF). He dramatically responded, his white blood cell became normal within 1 day and persisted until discharge. G-CSF can stimulate myelopoiesis and decrease bone marrow transit time from 6.4 to 2.9 days, no effect on blood neutrophil circulatory half life or in the distribution between the marginal and circulating pools[15]. However, in the presented case, the recovery of agranulocytosis happened within 1 day, it is too early to be presumably due to effect of G-CSF.

Mechanisms for leucopenia including thrombocytopenia in dengue hemorrhagic fever are multifactorial, some researchers demonstrate direct suppression on hematopoietic stem cells by dengue virus[16-18] while others show increased adhesion of neutrophil including platelet to dengue-infected endothelial cells until resulting neutropenia or thrombocytopenia[19]. In the presented case, the very rapid recovery of agranulocytosis favored the peripheral destruction.

The severity of thrombocytopenia, hemoconcentration, as well as coagulopathy, not including leucopenia or neutropenia, always account for poor prognosis. In the presented case, the nadir was on D5 while the platelet was still > 100,000/mm^3. After G-CSF treatment, white blood cell count was up to normal but the platelet was continually lowered. However at the lowest level, the platelet was not low enough to result in spontaneous bleeding. At the convalescent stage, normal white blood cell and platelet count were persistently sustainable.

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การลดต่ำมากของเม็ดเลือดขาวชนิดมี แกรนูล ในโรคไข้เลือดออก: ภาวะที่ถูกละเลย

สมชาย อินทรศิริพงษ์

ภาวะเม็ดเลือดขาวต่ำพบได้บ่อยในไข้เลือดออก แต่ภาวะเม็ดเลือดขาวต่ำมาก (agranulocytosis) ยังไม่มีรายงานมาก่อน ภาวะนี้เพิ่งพบในผู้ป่วยชายไทยอายุ 14 ปี มาตรวจด้วยอาการไข้ และท้องเดิน 3 วัน ระหว่างอยู่ในโรงพยาบาล มีภาวะเลือดเข้มข้นและเกล็ดเลือดต่ำ ร่วมกับผลการตรวจภูมิต่อต้านไวรัสเดนกี่ให้ผลบวก จึงได้รับการวินิจฉัยว่าเป็นไข้เลือดออก ในวันที่ 5 ของไข้ ผู้ป่วยมีเม็ดเลือดขาวต่ำมาก ทั้งที่ไม่ได้กินยาขนานใดมาก่อน จึงให้การรักษาด้วย filgrastim และยาปฏิชีวนะ เม็ดเลือดขาวกลับเป็นปกติในวันรุ่งขึ้น และทรงตลอดจนวันกลับบ้าน