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CLINICAL AND LABORATORY EXAMINATIONS ON A CASE OF "HEMORRHAGIC FEVER" FOUND IN SURABAJA, INDONESIA, IN 1968*

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Susumu HOTTA, Kichihei MIYASAKI, Manabu TAKEHARA, Yoshio MATSUMOTO, Yoshitami ISHIHAMA, Mikio TOKUCHI, BIROUM NOERJASIN, L. PARTANA, and I. SISWADI. *Clinical and Laboratory Examinations on a Case of "Hemorrhagic Fever" Found in Surabaja, Indonesia, in 1968.* Kobe J. Med. Sci. 16, 203-210, December 1970——In August 1968, a three-year-old native boy in the City of Surabaja, East Java, was found to have symptoms characteristic of "hemorrhagic fever" (HF), with sudden onset of high fever, vomiting, and diarrhea. Small petechiae were manifested on the extremities and face. Tourniquet test was strongly positive. The blood platelets were extremely decreased. Hepatomegaly and disturbance of liver functions were noted, but no jaundice was observed. Thereafter, a shock-like state appeared which lasted for two days. Fortunately the patient gained a complete and uneventful recovery by medical treatments.

Serological tests indicated that the patient's hemagglutination-inhibition (HI) titers against dengue types 1, 2 and 4, as well as against Japanese encephalitis and yellow fever viruses were initially low and later elevated, showing especially a 16 times rise of titers against dengue type 2. Isolation of the virus from the patient's blood, however, was not unequivocal.

Based on these data, and compared with previous descriptions on the HF syndromes found in Southeast Asian areas such as Manila, Bangkok and Singapore, the Surabaja case was diagnosed as HF which was presumably caused by infection of dengue type 2 virus. This is perhaps the first case clinical-virologically confirmed as HF in Indonesia.

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INTRODUCTION

"Hemorrhagic fever" (HF) is a generalized infection characterized by hyperpyrexia, hemorrhage (capillary and/or massive) and disturbances of one or more organs, especially of liver and kidneys, often accompanied by shock syndromes. During the past decades, apparently different categories of HF have been recognized in various parts of the world. [2) 3) 5) 6) 7) 16) 20) 21) 30) 31) 33)] Among them one type of HF has appeared in Southeast Asia and Western Pacific. The first description on HF of this category is perhaps that by Quintos et al[27)] who observed outbreaks of the typical cases in Manila, Philippines. Thereafter, similar epidemics occurred in Bangkok, Thailand,[12) 15)] and then in other areas such as Singapore, Vietnam, Cambodia, Ceylon, Calcutta, etc.[8) 9) 10) 22)] While some of the HF's hitherto recognized are yet etiology-unknown, it has recently been established that the Southeast Asian HF is mosquito-borne and intimately connected with certain arboviruses, especially those of dengue (of various types) and chikungunya (CH).[4) 10) 11) 13) 24)]

Although special interest has been focused to the disease since then, no such case has been reported in Indonesia. This seems to be rather curious because Indonesian islands are not far from the HF-prevalent areas aforementioned and are abundant in *Aedes* mosquitoes, vectors of the dengue and CH viruses. On the other hand, our previous data concerning HI tests with sera from Indonesian residents clearly indicated that anti-dengue and anti-CH antibodies are distributed in representative geographic parts of Indonesia, suggesting possible existence of mosquito-borne HF's in the same areas.[17) 18) 19)] Moreover, one of the present authors (L. Partana) and her colleagues observed a number of clinically suspected HF patients in Surabaja, East Java, during the past several years.[25)]

In 1968, when the Kobe University Medical Team visited Indonesia, we were informed of occurrence of HF-like diseases in Surabaja and cooperative works of Indonesian and Japanese scientists were immediately started. A typical case was examined in detail, and the clinical and laboratory data thereof will be reported in the present paper.

PROTOCOLS

Patient: Three-year-old native boy, in Surabaja City, East Java.
Chief complaint: Fever, diarrhea, and vomiting.
Family history, and Past history: Non-contributory.
Present illness:

There was a sudden onset of high fever and diarrhea on August 16, 1968. The patient came to the Pediatric Clinic of Dr. Soetomo Hospital, Surabaja, at 10 a.m. on August 19. At that time he had 4–5 bouts of diarrhea daily but without fever and went back home with a tentative diagnosis of gastroenteritis. At 11 p.m. of the same day, however, vomiting, insomnia, high fever, and sweating occurred suddenly and the patient was immediately admitted to the Hospital.

Findings upon admission on the fifth day of illness

(A) *Physical examinations*

The patient was underdeveloped and undernourished at the time of physical examinations. Body weight was 8.2kg. On inspection, he was found to be restless and there was a profuse sweating. Small, barely detectable petechiae were found on the extremities and countenance. Bulbar conjunctivae were free of jaundice and palpebral conjunctivae were not anemic. Pupils were equal in size and the light reflex was normal. Pulse was regular with a rate of 120/min. Blood pressure was 100/70 mmHg, respirations 36/min. and rectal temperature 38.2°C. Percussion revealed normal cardiac dullness; cardiac sounds were somewhat distant but clear. The lung fields were clear by auscultation and percussion. The abdomen was flat, liver was palpable 2 finger-breadths below the right costal margin, but neither kidneys nor spleen were palpable. No lymph-nodes were palpable. Neurological examinations revealed no abnormalities. The tourniquet test was positive.

(B) *Laboratory tests*

Urine: pH 5.5, protein (±), sugar (−).
Feces: Chocolate colored melena containing abundant leucocytes and mucus. *Ascaris* ova were found.
Peripheral blood: RBC 5,000,000/mm^3; Hb 12.6g/dl; WBC 12,000/mm^3.
Differential counts: Eosinophils 0%, basophils 0%, band form neutrophils 10%, polymorphonuclear neutrophils 46%, lymphocytes 30%, and monocytes 14%. Atypical lymphocytes, resembling plasma cells or monocytes, with basophilic cytoplasm and many vacuoles, were noted. Platelets markedly decreased (9,000/mm^3).
Cerebrospinal fluid: Normal pressure; cell counts 3; protein 20mg%; and negative Nonne-Apelt and Pandy reactions.
Liver function tests: Serum total protein 5.8%; serum total cholesterol 150mg/dl; serum alkaline phosphatase about 4 Bodansky units; T. T. T. (+ + +); and elevation of SGOT and SGPT.
Sternal bone marrow picture: M-E ratio was 3 : 1 and normal. There were abundant megakaryocytes with the nuclei containing many vacuoles, and naked nuclei were seen occasionally. Promegakaryocytes were also found abundantly.

Course of illness and treatment

Figure 1 shows overall course of illness and medical treatments. Shortly after admission, petechiae increased in number with a persistent thrombocytopenia (9,000–10,000/mm^3) and high fever (38–40°C). Blood pressure was unstable, ranging between 120/70 to 90/50 mmHg, occasionally dropping to an unmeasurable level, and the patient went into a shock-like state. Hepatomegaly was continually present.

Adrenocortical hormones and tetracycline were administered and intravenous drip infusions of 5% glucose and physiological saline were given. On August 20 and

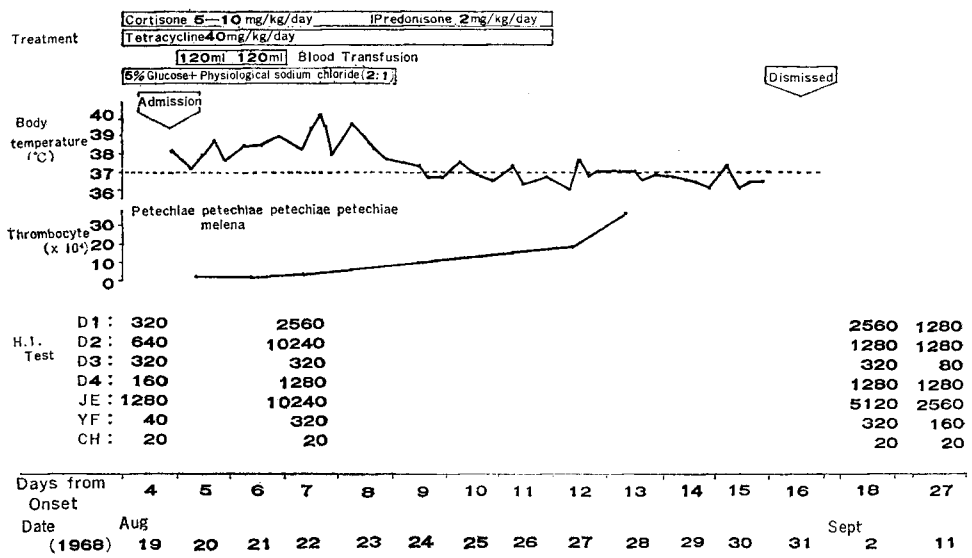
21, while the patient was still in the shock state, excreting large amount of melena, preserved blood (120 ml per day) was transfused.

On the seventh day of illness, August 22, petechiae and high fever had still persisted. Despite continued disturbances of the liver functions, hepatomegaly subsided. Blood pressure became stable, and the patient started to drink milk. Thrombocytes increased to 31,000/mm^3. From the 8th day of illness, temperature started to return towards normal and petechiae began to decrease in number.

In the differential leucocyte counts, the ratios of neutrophils and lymphocytes fluctuated, but with a persistent leukocytosis. There was a marked thrombocytopenia during the initial stage, but recovery to 165,000/mm^3 occurred by the 12th day of illness. Monocytes in the peripheral blood, on the other hand, increased in the initial stage but later decreased gradually. Morphological features of the megakaryocytes were essentially normal.

On the thirteenth day of illness, the disturbance of liver functions had almost subsided and neither fever nor new petechiae appeared. The platelet count was 357,000/mm^3. Although his general condition was still poor, the patient was discharged on August 31 (the 16th day of illness). Body weight at that time was 8.6kg. The subsequent course was uneventful.

Fig. 1 Clinical course and medical treatments of a "hemorrhagic fever" patient (Surabaja, 1968)



Serological tests

HI titers of the patient's sera from early and later stages were measured by the method described previously.[17] Antigens employed included those of dengue types 1 to 4 (D1, D2, D3, D4), Japanese encephalitis (JE), yellow fever (YF) and

chikungunya (CH).

As shown in the Figure 1, significant rises of HI titers between the 4th and 7th days of illness were noted against D1, D2, D4, JE and YF antigens, amongst which the rise of anti-D2 antibodies was highest, i.e., 16 times elevation. It was interpreted, at least from the serological point of view, that D2 virus was principally involved in the present illness.

Virological examinations

Isolation of etiologic virus or viruses from the patient was tried. Defibrinated blood, heparinized blood, and bone marrow (aspirated from the sternum and emulsified in Hanks' balanced salt solution of 10 times volume) were collected on August 21 (the 6th day of illness) and inoculated into brains of suckling and 2-week-old mice and into established African green monkey kidney cell cultures. The inoculated mice and cell cultures were carefully observed for 5 to 6 weeks thereafter.

From individual mice which showed debility and/or paralytic signs, the brains were removed, emulsified in Hanks' solution and injected into brains of other mice. "Blind passages" through mouse brains were also carried out. Although some of the mice in the first and second passages exhibited debility or suspected paralysis of the extremities, it was not successful to get viral agent(s) completely adapted to the mouse brain. No attempt was made to test possible development of anti-dengue immunity in the surviving mice by challenging them five weeks after inoculation with 100 x LD_{50} dengue viruses of known types.[14) 28) 29)]

In all the inoculated cell culture tubes, no cytopathic effect (CPE) was observed. Culture fluids taken from the inoculated tubes at the end of observation periods were injected into suckling mice intracerebrally, but no viral agent was recovered.

DISCUSSION

The symptoms of the present case are well compatible with major signs of the mosquito- borne HF which have been reported by previous investigators. Abrupt onset of high fever, petechiae, coffee-ground vomiting, melena, and shock syndromes, etc. were typical of HF; marked thrombocytopenia[23) 26) 32)] and disturbances of liver functions[1)] were also revealed. According to Hammon et al,[12)] differences were noted between the clinical signs of HF patients observed in Manila and Bangkok: (i) Hepatomegaly was common in Bangkok and absent in Manila; (ii) red-purple blush of the skin (which did not fade on pressure) was common in Manila and rare in Bangkok; (iii) the similar statements could be made relative to epistaxis, i.e., it was common in Manila and rare in Bangkok; and (iv) classical dengue-like rashes (fleeting and easily missed unless searched for carefully) were occasionally seen in Bangkok only. So far as concerning these criteria, our Indonesian case seems to resemble those in Bangkok rather than those in Manila.

The serological tests with the patient's serum indicated significant elevation of HI titers against certain group B arboviruses, especially type 2 dengue, during the febrile stage. Intimate correlation of the present illness with infection of the arbo-

virus(es) was suggested. It is to be pointed out in this connection that the HI titers were fairly high already in the early stage of illness. Whether such antibody patterns were an indication of the hypersensitivity state caused by the viruses under study as proposed by previous investigators[8) 9)] was not clear, since no other data were available to support the hypothesis. The fact that the patient was given blood transfusion may have to be considered; however, it appears difficult to explain the high elevation of the HI titers and their duration thereafter as direct effect of the blood transfusion.

In attempts to isolate etiologic agents (possibly dengue viruses in this case), blood and bone marrow emulsion taken from the patient during the febrile stage were injected into mice intracerebrally and brain passages in mice were performed thereafter. The same materials were inoculated also into established African green monkey kidney cell cultures. Although suspected signs of infection such as debility and/or slight paralysis were exhibited in some of the inoculated mice of the first and second passages, no complete adaptation of any virus to mice was successful. Nor any viral agent was recovered from the inoculated cell culture fluids. The results are not considered to be fully failed, however; previous experiences have been reported that primary isolation of dengue and related viruses from typical HF patients with shock syndromes, especially those on the 4th day of illness or later, is extremely difficult.[4) 22)] Further trials are therefore necessary to establish the etiology of "Surabaja HF" by direct isolation of viruses. Still the serological tests were well indicative of the involvement of group B arboviruses, particularly type 2 dengue, in the present HF syndrome. In this limitation, the present case is perhaps the first one clinical-virologically confirmed as HF in Indonesia.

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