A POSSIBLE CASE OF FATAL APLASTIC ANEMIA ASSOCIATED WITH VIRAL HEPATITIS

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Viral hepatitis rarely involves other organs, especially the bone marrow. During the past decade, a number of cases of mostly fatal pancytopenia associated with hepatitis have been published.(2, 8, 13, 14, 16) The hepatitic disorder appeared to be viral in origin, clinically as well as morphologically. Report herein, is an additional case of such association.

Case Report :

A twenty year-old Thai man was in good health until six weeks prior to admission when he developed fever, mild jaundice, dark-colored urine, and light-colored feces. During this time, he still maintained his daily routine A few weeks later, however as these symptoms persisted, accompanied by general weakness, he went to visit a local physician who prescribed "cold capsule" (containing phenacetin 0.05 gr, sodium phenyldimethylpyrazolonemethylaminomethone sulphonate 0.1 gr., ascorbic acid 0.05 gr., -p-dilorobenzyl-2 pyrrolidylmethylbenzimidazol hydrochloride 0.02 gr., and ephedrine hydrochloride 0.0 gr.) The total amount of drug taken was six capsules in three days. There was no improvement of the patient's condition. He then went to another clinic and received tetracyclin and streptomycin intramuscularly, again without any improvement. He was therefore admitted to Chulalongkorn hospital. The physical examination revealed a markedly icteric patient. The blood pressure was 110/70 mm. Hg. The pulse was 92/min, and the respiration, 30/min. He had a body temperature of 40 degree centigrade. The liver edge was felt three finger-breadth below the right costal margin, without tenderness. Other systemic examinations were all normal. The hemoglobin was 2.7 gm. and red cell count was 1.2 millions per cubic millimeter. The white cell count was 800 with 40 per cent neutrophils and 60 per cent lymphocytes. The reticulocyte count was 0.4 per cent and there was no platelet in the count. Coomb's test was negative, both in the direct and

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indirect methods. Paper electrophoresis revealed an A type hemoglobin. There was 4 plus bile in the urine. The urobilinogen was positive in 1 : 128 dilution. A total serum bilirubin was 9.3 mg. with a direct action bilirubin of 3.8 mg. per 100 ml. The cephalin flocculation test was 3 plus in 48 hours; thymol turbidity was 1.5 units, and zine turbidity, 14.2 units. The serum alkaline phosphatase was 61.0 Bodansky units. The SGOT and SGPT were 1,400 and 1,050 units respectively. The serum albumin and globulin were 4.3 gm and 1.5 gm per 100 ml. The prothrombin time was 19 seconds (control 12 seconds). The bone marrow was hypoplastic with maturation arrest. Most of the cells were promye locytes and myelocytes. Only a few polymorphonuclear cells were seen. The erythroid cells were predominantly late erythroblasts and early normoblasts. The mega karyocytes appeared adequate, but they were immature, No extrinsic cells were noted. (Fig.1)

During the first week in the hospital, tha patient recievd six blood transfusions and 60 mg. of prednisolone per day. The general condition was not improved and jaundice was progressive, The body temperature ranged between 38.5 – 40 degrees centigrade. Repeated hemogram showed a 7.8 gm. hemoglobin; the white cell count was 100 per cubic millimeter with 55 per cent neutrophils and 45 per cent lymphocytes. The platelet count was 2,000 per cubic millimeter. The serum alkaline phosphatase was

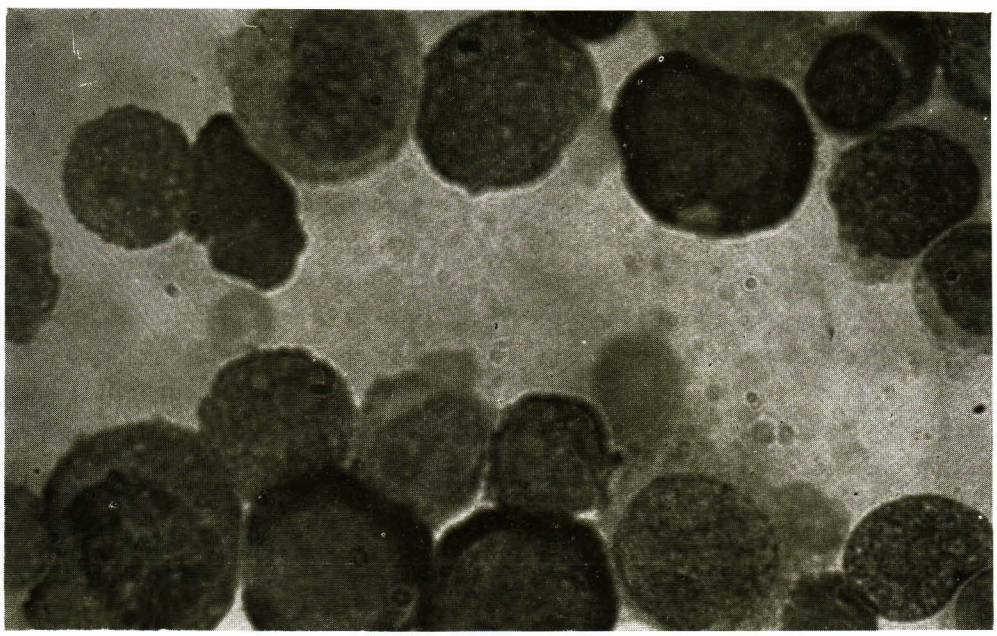

Fig. 1: Bone marrow, first aspiration, showing most of the cell are promyelocytes; myclocytes and erythroblasts. Wright stain x 900

70.3 units. Urine culture grew Escherichia coli. At the end of the week, the patient developed upper respiratory tract infection, despite administration of antibiotics. A second marrow aspiration was performed two weeks after admission. It showed a relatively hypocellular arrow as compared to the first, All cellullar components were depressed, particularly the myeloid cells. (Fig. 2). The hemoglobin went down again to 5.1 gm. and the red cell count was 1.4 millions per cubic millimeter. The leucocyte count was 300 per cubic millimeter and the platelet was 15.000 per cubic millime ter and the reticulocyte, 0.1 per cent. Prednisolone was then increased to 100 mg/day and, in addition, 100 mg. of testosterone per day was given. In spite of the treatment, the patient's condition deteriorated progressively. Jaundice and fever persisted and he developed epitaxis and melena. The liver became larger with slight tenderness. The coagulogram performed at the time of active bleeding revealed a prolonged prothrombin time, of 18 seconds. A small, soft, cervical lymph node was palpated on the right side. The biopsy diagnosis was reactive hyperplasia of the lymph node. Repeat liver function test revealed a total billirubin of 10.2 mg. with 5.0 mg. per 100 ml. direct action. The SGOT and SGOT were 440 and 775 units respectively. On his last day, the body temperature was 40.5 degrees centigrade. He developed mental confusion and respiratory dis-

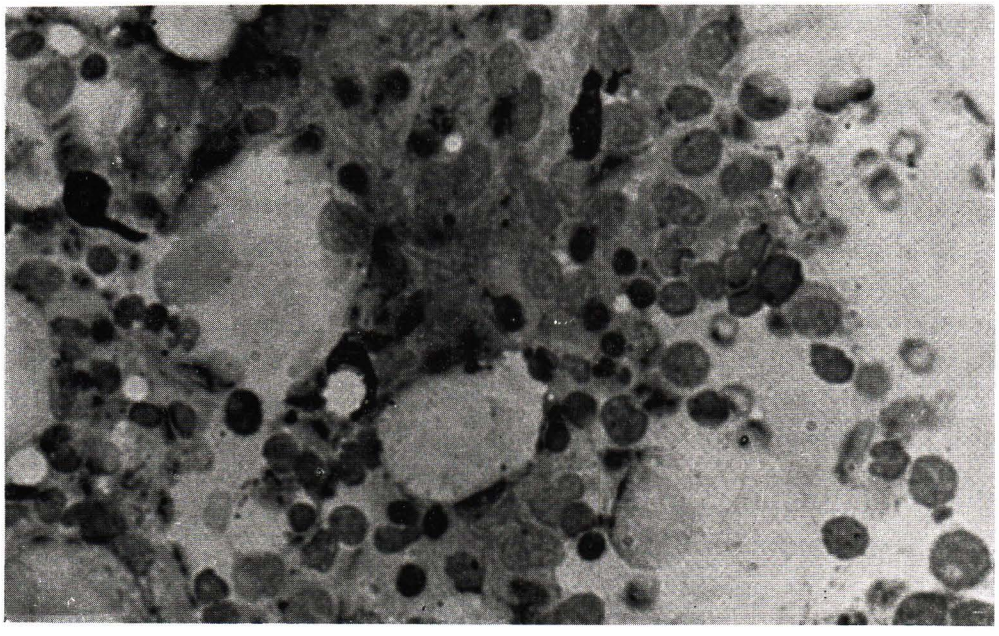

Fig. 2: Bone marrow, second aspiration, showing marked hypocellularity, especially of the myeloid series. Wright stain, x 400

tress and expired, twenty — one day after the admission. The last hemog ram prior to death showed a hemog lobin of 5.4. gm, the white cell of 700 per cubic millimeter. Platelet and reticulocyte were not found.

At autopsy, there was marked jaundice of the skin and the sclerae. Multiple petichiae and ecchymoses of the skin of the body and extremities were noted. A considerable amount of clear yellowish fluid was present in the pleural cavities as well as in the abdominal cavity. The liver weighed 2,100 grams. It was yellowish and soft. The surface was smooth and tense. The cut surface showed yellowish red mottlings. Histologically, there was marked distortion of the hepatic cell plates. Extensive liver cell necrosis was noted. (Fig. 3) The remaining hepatocytes showed frequent binucleation, microvesiculation and intrahepatic cholestasis. (Fig. 4) Leucocytic infiltration in the portal tracts was strikingly increased, comprised mainly of mononuclear cells and some neutrophils. Eosinophilic bodies in the hepatic sinusoids were observed. The Kupffer's cells showed proliferation. No eosinophils or granulomatous reactions were noted. The bone marrow showed extreme hypocellularity of all cellular components. There was evidence of erythrophagocytosis. (Fig. 5)

Comments

Twenty-six cases of pancytopenia associated with hepatitis have been reported in the literature during the past decade.[2,6,8,12,13, 6] Except for the two cases in which this association occurred in middle age[6,12] patients all of the others were in the younger age group, ranging from three and a half years old to twenty-two, Twenty of the total cases were male. The duration between the onset of hepatitis and pancytopenia varied from simultaneously to twenty-six weeks (Table I). In most cases, however, the occurence of pancytopenia developed after hepatitis had already subsided. In our case, pancytopenia developed concomittently during the course of hepatitis.

The most unusual liver function test finding in this patient was the very high level of alkaline phosphatase, which was 61 units on the day of admission. It was 70.3 units one week later. Zimmerman and West[18] found about 5 % of patients with viral hepatitis had an elevated value of serum alkaline phosphatase above 15 units. They believed that the increase of the enzyme was a result of cholestasis despite the fact that, morphologically, there was only little evidence of hepatocellular damage. Never had any series reported this high level. In our case there was a marked hepatocellular injury with evidence of intrahepatic cholestasis at autopsy.

The worsening of jaundice in this patient may have been due to hepatitis superimposed on by hemolytic complication of septicemia. The admi-

Fig. 3 : A section of liver showing extensive necrosis. H & E x 100

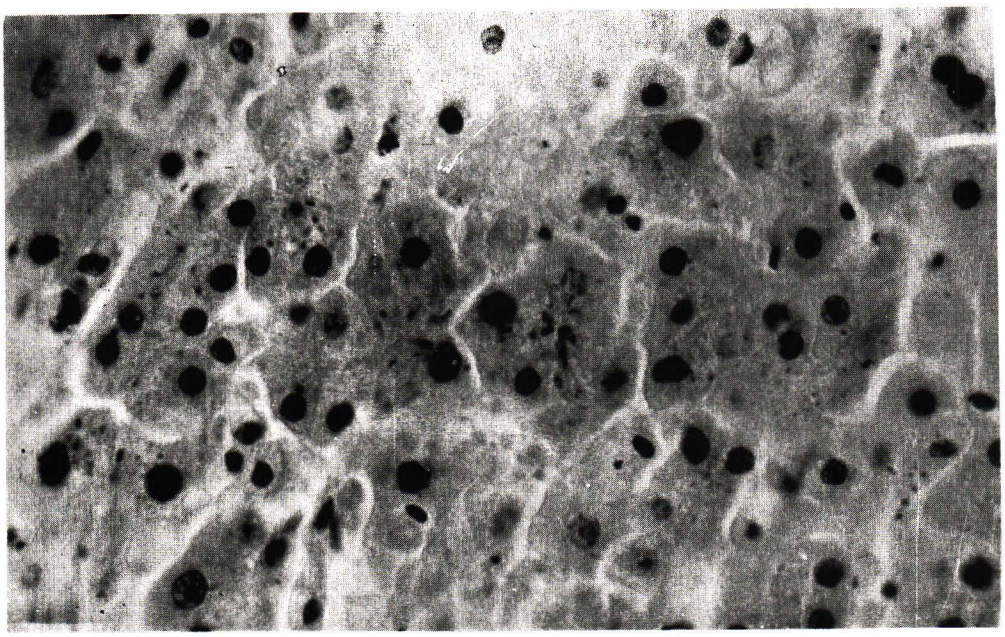

Fig. 4 : Liver cells showing intrahepatic cholestasis are shown in the middle field, H & E x 400

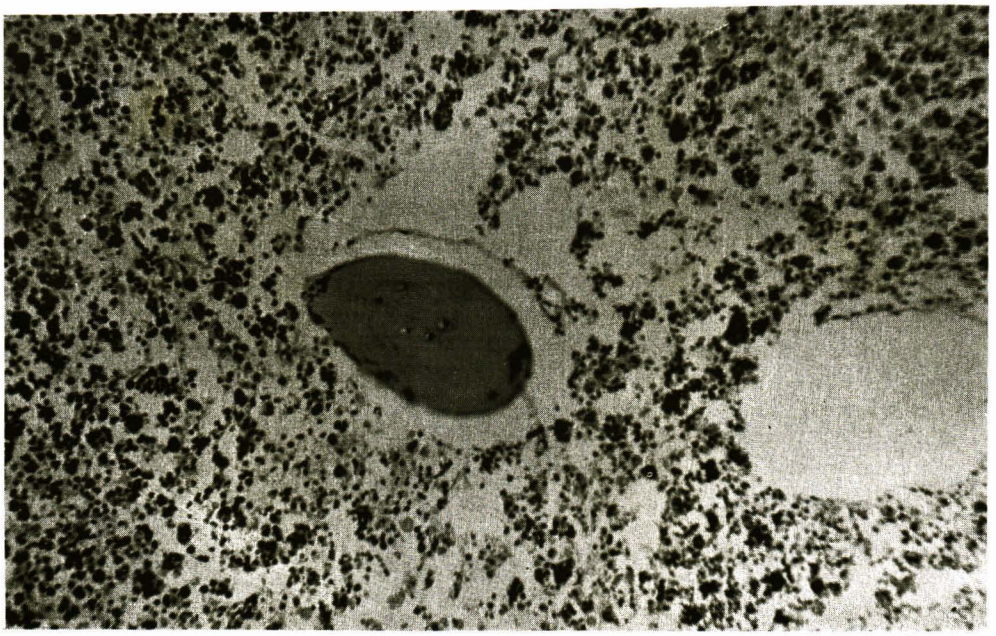

Fig. 5: The bone marrow shows hypocellularity involving all cell components. H & E x 100.

nistration of phenacetin and pyrazolone may or may not be an important causative factor in the development of the malady. It is interesting to note the indirect relation of the serum billirubin and the SGOT level. When the billirubin was elevated from 9.3 to 10.2 mg. the level of SGOT went down from 1,400 to only 440 units.

It was unfortunate that the patient had taken a bone morrow toxic drug during the course of illness, before admission. The total dose of phenacetin was 0.9 gr. and of pyrazolone, 0.6 gr. However, it is clear that all the drugs were taken after jaundice had persistently developed. Streptomycin as a possible cause of pancytopenia was reported by Deyke and Wallace[3] in 1948. Thig drug, as well as tetracyclin, were, likewise, given after the onset of jaundice.

According to Scott and associates[15] three etiologic mechanisms producing acquired aplastic anemia were suggested, namely; deficiency of a certain essential factor for erythroid stimulation, direct marrow toxicity and an autoimmune reaction. It has been suggested that it is possible to deplete the bone marrow suddenly by an enormously increased peripheral destruction of blood cells. It is possible that the virus of hepatitis itself may be "cytotoxic". However, if only agents capable of producing bone marrow aplasia in exposed persons are considered to be "true cytotoxins", the hepatitis virus, affecting only a few (as is true with most other agents

Table I : Previously Reported Cases of Hepatitis and Pancytopenia

Source	Age / Sex	Interval between hepatitis and pancytopenia (weeks)	Survival from onset ot hepatitis (weeks)
Lorenz, Quaiser 1955 (9)	9 / M	6	24
Korsan 1956 (6)	22 / M	2	5
Dische, Golding 1957 (4)	22 / M	unclear	10
Beickert, Siering 1958 (1)	19 / F	5	7
Deller et al 1962 (2)	17 / M	7	22
Kramer 1963 (7)	48 / F	12	alive
Pitcher and Spence 1963 (12)	64 / F	7	13
Simpson 1963 (17)	8 / F	26	51
Levy et al 1965 (8)	11 / M	3	13
	19 / M	5	7
	4 / M	1	26
	14 / M	7	11
	11 / F	7	13
Schwarz et al 1966 (14)	8 / M	9–10	22
	3.5 / M	0	alive
	3 / M	16	alive
Rubin, Gottlieb & Vogel 1968 (13)	17 / M	3	9
	10 / M	3–4	6
	13 / M	8	4
	18 / M	2	3
	8 / F	3–4	14
	11 / F	9	26
	20 / M	5	8
	7 / M	7	alive
	2 / M	20–24	alive
	8 / M	?	alive

incriminated as bone marrow depressants), must act through some other mechanisms. It has been postulated that altered liver function may permit an endogenous toxin to circulate and destroy marrow, but such a substance has not yet been discovered. It is more likely that the "toxin" effect on the bone marrow in these cases depends on additional host factors, such as idiosyncrasy, hypersensitivity and autoimmunity.(18)

The latent period between hepatitis and pancytopenia, which may extend to six months, makes the hypothesis of chromosomal damage to the hematopoietic system attractive. (Table 1). Recent demonstrations that the serum of patients with infectious hepatitis, both in the acute(10) and convalescent phases(5) produces chromosomal abnormalities in cultured leukocytes from normal persons, lends credence to this hypothesis.

Summary

A case of fatal pancytopenia associated with hepatitis, probably of viral in origin in twenty year old Thai was reported. The causal relationship of these disorders is discussed.

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