THE TURKISH JOURNAL OF
PEDIATRICS
A HACETTEPE BULLETIN VOLUME 11/NUMBER 2/APRIL 1969

Aplastic Anemia After Hepatitis

A Case Report

Dr. İzzet Berkel M.D.*

Development of aplastic anemia following viral hepatitis is quite rare. Thirty-four such cases have been published since 1955,[1-13] and all but six ended fatally from complications of pancytopenia. Review of the reported cases suggests that the occurrence of hepatitis followed by aplastic anemia may be more than a coincidence.

In this paper a case of fatal aplastic anemia in a young boy which developed after viral hepatitis is reported.

Case Report

A seven-year-old Caucasian boy was admitted to Hacettepe Children's Hospital on January 21, 1963, with complaints of pallor, nose bleeding and excessive bruises of three weeks' duration. Three months prior to admission he complained of nausea, anorexia, and fatigue, and developed jaundice which was diagnosed as viral hepatitis by his physician. On bed rest, multivitamins and tetracycline the jaundice disappeared in 10 days. Four weeks after the onset of hepatitis, he had repeated nose bleeding, bruises, pallor, fever and bloody vomiting. He was admitted to a local hospital where multiple blood transfusions, penicillin and tetracycline were given. After

From the Department of Pediatrics, Research Institute of Child Health, Hacettepe University, Faculty of Medicine, Ankara.
* Associate Professor of Pediatrics and Pediatric Hematologist

four weeks' hospitalization he was discharged, at which time he experienced fatty stools, coughing and fever. Then on January lst, 1963, the patient was seen in the out-patient clinic of Hacettepe Children's Hospital. He was pale with scattered petechiae over the body. The pharynx was hyperemic, but the rest of the physical examination was negative. Since the parents refused to admit the patient, he was started on prednisolone, oral penicillin and tetracycline. Because of severe anemia, he was given a blood transfusion at the local hospital. On January 17, 1963, he developed nose bleeding which continued until admission to Hacettepe Children's Hospital. His past history revealed no known exposure to drugs or toxins, and there was no history of injection before hepatitis.

Physical examination on admission revealed pallor with oozing blood in both nostrils. His height and weight were under the three percentile 13 cm and 18 kg respectively. Temperature was 36.5°C, pulse was 130 per minute and respiration was 28 per minute. The pertinent physical findings were scattered petechiae and ecchymosis on the trunk and extremities and a grade III°/VI systolic murmur over all the cardiac areas. On admission hemoglobin was 5.34 gr / 100 ml. WBC 800 per cmm (with 72 per cent neutrophils), and platelets 24.000 per cmm. The bone marrow was hypocellular with an increased number of lymphocytes. Megakaryocytes were not seen. The mycloid and erythroid elements were also absent.

Direct and indirect Coombs tests were negative. Serum cholesterol was 125 mg / 100 ml with a free fraction of 40 mg / 100 ml. Thymol turbidity test was one unit. The patient was given prednisolone 2 mg/Kg and blood transfusions. Repeat bone marrow specimens (three weeks and six weeks after admission) were also hypocellular and fatty with absent megakaryocytic, myeloid and erythroid series. Lymphocytes were increased in number. Dianobol was added to the corticosteroid therapy and two weeks later this was changed to methyltestosterone (2 mg/Kg). He had multiple blood transfusions. On June 1, 1963, 18.5 weeks after admission, the patient developed jaundice. Total bilirubin was 11.2 mg / 100 ml with a direct fraction of 7.5 mg / 100 ml. Testosterone was discontinued because of its suspected role in the etiology of jaundice. On June 21, 1963, total bilirubin was 2 mg / 100 ml and the direct fraction was 0.7 mg / 100 ml. On July 13, 1963, the patient developed high fever and moist rales in the lung fields. Despite antibiotic therapy, he died of sepsis and bleeding on July 20, 1963, six months after admission and nine months after the onset of hepatitis. Permission for postmortem examination was not given by the parents.

Discussion

In 1955 Lorenz and Quaiser, and in 1956 Kosan, reported two cases of pancytopenia which developed six and two weeks respectively after the onset of viral hepatitis in nine and 22-year-old males. [1 2] In the following years new case reports were published, [3-13], and including our own we were able to count 35 such cases in the literature, although the number may be higher with recently published case reports. The male preponderance was striking, but no explanation has been found for this. All but two were children or young adults aged between two and 22 years. The period between the onset of hepatitis and the development of pancytopenia varied from one to nine weeks in all cases except two (Simpson's and the ninth case of Rubin et al). [6 13] It was noticed that our patient had pancytopenia four weeks after the onset of hepatitis. All reported patients, including ours, showed markedly hypocellular bone marrow specimens involving myeloid, erythroid and magakaryocytic series.

It is noteworthy that some patients exhibited leukopenia and thrombocytopenia during the acute stage of the hepatitis.

Our patient died six months after the diagnosis of aplastic anemia, which did not respond to combination therapy of androgen and corticosteroids. Only six patients (one adult and five children) were still alive after androgen and corticosteroid therapy, the others were all dead by the time of reporting.[13] In those who lived, bone marrow aplasia may have been temporary and except for massive liver necrosis, the main problem is protection from bleeding and infection.

The appearance of pancytopenia following viral hepatitis may not be a coincidence. It is conceivable that the sequence of events may be causally related with the assumption of a viral etiology. Possibilities for the association of aplastic anemia and hepatitis may be as follows:

1 — A direct effect of the virus;

2 — Failure of the liver to detoxify a myelosuppressive substance;

3 — An autoimmune mechanism;

4 — A genetic alteration in hematopoietic cells.

Infectious hepatitis is initially considered as a systemic disease and the virus might infect the bone marrow.[14] Invasion of the hematopoietic cells in the state of mitosis by a virus prevents their normal progression to maturity or even causes their death. Pancytopenia may develop from as early as one week, to 10 or more weeks after the initial viral alteration of

the precursor marrow cells[15] Irreversible marrow damage takes place if many young dividing blood cells are infected. Leukopenia is common during the period of viremia in infectious hepatitis.[16] Thrombocytopenia of varying degrees is also reported because of viral invasion of the bone marrow.[17] It is reported that other viruses such as mumps, rubella and dengue fever temporarily depress one or more hematopoietic elements of the bone marrow.[18-20] Infection of mice with the mouse hepatitis virus (MHV-3) produces hepatitis histologically quite similar to one seen in viral hepatitis in man. Degenerative changes in all hematopoietic cells consequently result in pancytopenia.[21] Similar liver damage in mice can be seen after infections with the Trinidad strain of Venezuelan equine encephalitis, in which case the virus can be recovered from the bone marrow when it can no longer be demonstrated in other organs.[22]

Another possible explanation of the relationship between infectious hepatitis and progressive bone marrow depression is that drugs used during the acute stage of the hepatitis may not be metabolized as rapidly as by the normal liver cells. This functional liver disturbance may lead to increased drug levels which might become toxic to the bone marrow. Even corticosteroids could not be metabolized well by a sick liver in infectious hepatitis, and high levels of this drug can eventually result in a fatty bone marrow.[15] The toxic effects of penicillin, tetracycline and polyvitamins on the bone marrow could not definitely be claimed in the case of our patient.

Although there is as yet no supporting experimental evidence, it has been suggested that during the course of infectious hepatitis, production of the essential factors for normal hematopoietic activity by the liver is also depressed.[8] This insufficient production may effect the bone marrow cells. A mild hemotytic anemia frequently develops during the course of infectious hepatitis.[23]

Development of an antibody against one's own tissues, or autoimmunity, seem to be unlikely, because it has never been convincingly incriminated in aplastic anemia. In only one previously reported case of this syndrome were any manifestations of an autoimmune hematologic disorder found.[3]

Lastly, the possibility of a genetic alteration in hematopoietic cells caused by chromosomal damage has to be considered. In fact, the serum of patients with infectious hepatitis both in the acute and convalescing phase produces chromosome abnormalities in culture leukocytes from normal persons. [24] [25] Observations on the possible epidemiologic association of hepatitis and Down's syndrome also suggest that the hepatitis

virus results in chromosomal damage.[26] Serum from patients with infectious hepatitis has an inhibitory effect on the cultured leukocytes of normal individuals, just as it has, in addition, on cultures of leukocytes from patients suffering from hepatitis.[24]

Summary

A case of aplastic anemia following infectious hepatitis is reported. Possibilities for the association of aplastic anemia and hepatitis are discussed and the related literature is briefly reviewed.

REFERENCES

1– Lorenz, E. and Quaiser, K.: Panmyelopathie nach Hepatitis epidemica, Wien Med. Wchnschr. 105: 19, 1955.

2– Kosan, N.: Pancytopenie als Komplikation einer Hepatitis und Ursache einer Leberdystrophie, Med. Monatschr. 10: 794, 1956.

3– Beickert, A. and Siering, H.: Immunpancytopenie mit Auftreten heterophiler Antikörper bei akuter Hepatitis epidemica kompliziert durch eine schwere Myocarditis, Acta Haemat. (Basel) 19: 51, 1958.

4– Deller, J.J., Jr., Cirksena, W. J. and Marcarelli, J.: Fatal pancytopenia associated with viral hepatitis, New Eng. J. Med. 266: 297, 1962.

5– Pitcher, C. S. and Spence, E. M.: Fatal marrow aplasia complicating infectious hepatitis, Brit. Med. J. 1: 171, 1963.

6– Simpson, K.: Infective hepatitis and marrow aplasia, Brit. Med. J. 1: 473, 1963.

7– Kramer, A.: Panmyelopathie und virus hepatitis, Acta Hepatosplenol. 10: 228, 1963.

8– Schwarz, E., Baehner, R. L. and Diamond, L. K.: Aplastic anemia following hepatitis, Pediatrics 37: 681, 1966.

9– Castelli, S. and Bersani, S.: Un nuovo caso di pancitopenia aplastica acuta insorto durante il decorso di epatite virale, Riv. di Clin. Ped. 78: 445, 1966.

10– Ascione, A., Bruzzese, L., and Guinti, G.: Giorn. Malat. Inf. Paras. 12 bis Dicembre 1962 (cited by Ref. 9).

11– Leinweber, B. et al: Hepatitis und panmyelophthise, Deutsch Med. Wschr. 92: 841, 1967.

12– Aplastic anemia following viral hepatitis, Clinico-pathologic Conference, J. Iowa Med. Soc. 58: 948, 1968.

13– Rubin, E., Gottlieb, C. and Vogel, P.: Syndrome of hepatitis and aplastic anemia, Amer. J. Med. 45: 88, 1968.

14- Conrad, M.E., Schwartz, F. D. and Young, A.A.: Infectious hepatitis - a generalized disease, Amer. J. Med. 37: 789, 1964.

15- Editorial: Aplastic anemia after hepatitis, New Eng. J. Med. 273; 1165, 1965.

16- Havens, W. P., Jr. and Marck. R. E.: The leukocyte response of patients with experimentally induced infectious hepatitis, Amer. J. Med. Sci. 212: 129, 1946.

17- Woodward, T. E.: Thrombocytopenic purpura complicating acute catarrhal jaundice. Report of a case, review of the literature and review of 48 cases of purpura at University Hospital, Ann. Int. Med. 19: 799, 1943.

18- Famma, P. G. et al: Thrombocytopenic purpura complicating mumps, Brit. Med. J. 2: 1244, 1964.

19- Rausen, A. R. et al: Hematologic effect of intrauterine rubella, J. A. M. A. 199: 111, 1967.

20- Bierman, H.R. and Nelson, E.R.: Hematodepressive virus diseases of Thailand, Ann. Int. Med. 117: 170, 1966.

21- Piazza, N. et al: Hematological changes in viral (MHV-3) murine hepatitis, Nature 205: 1034, 1965.

22- Smith, T. J., McKinney, R. W. and Sawyer, W. D.: Isolation of Venezuelan equine encephalomyelitis virus by bone marrow culture, Proc. Soc. Exp. Biol. Med. 117: 271, 1964.

23- Raffensperger, E. C.: Acute acquired hemolytic anemia in association with acute viral hepatitis, Ann. Int. Med. 48: 1243, 1958.

24- Mella, B. and Lang, D. J.: Leukomitosis. Supression in vitro associated with infectious hepatitis, Science 155: 80, 1957.

25- El Alfi, O. S. et al: Chromosomal breaks in human leukocyte cultures induced by an agent in the plasma of infectious hepatitis patients, Hereditas 52:285, 1965.

26- Starck, C. R. and Fraumein, F., Jr.: Viral hepatitis and Down's syndrome, Lancet 1: 1036, 1966.