

Case Report

Hepatitis-Associated Aplastic Anemia

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ABSTRACT

There is a well-recognized relationship between aplastic anemia and viral hepatitis. Clinically apparent hepatitis precedes aplastic anemia by a period of weeks to months. Hepatitis is an infrequent cause of aplastic anemia and is usually severe and fatal if untreated. The clinical features and, particularly the response to immunosuppressive therapy strongly suggest that immune mechanisms mediate the marrow aplasia. The cause of the hepatitis is unknown, but it does not appear to be due to any of the known hepatitis viruses.

In this study we present two cases of hepatitis associated aplastic anemia (HAAA) at the ages of 10-11 years old.

They both received immunosuppressive therapy, Anti thrombocytic globulin and Cyclosporine. They achieved a persistent clinicohematological remission.

Keywords:

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Background and Aim

Hepatitis-associated aplastic anemia (HAAA) is a variant of aplastic anemia in which aplastic anemia follows an acute attack of hepatitis. The marrow failure can be severe and is usually fatal if untreated.(7), HAAA was first described in 2 case histories in 1955, and by 1975 more than 200 cases had been reported.(5-7), HAAA is not uncommon, with hepatitis documented in 2 to 5 percent of cases of aplastic anemia in the West(8,9) and 4 to 10 percent in the Far East.(10), In a Taiwanese study, a quarter of childhood cases of aplastic anemia were preceded by signs of hepatitis for which no cause

was clearly evident.(11), HAAA most often affects adolescent boys and young men who present with severe pancytopenia two to three months after an episode of acute hepatitis. There is no known association with blood transfusions, drugs, or toxins, and most patients have been seronegative for hepatitis A, B, and C.(12,13)

CASE REPORT

In this study, two children with HAAA admitted in children's Hospital during July 1999 to September 2003.

First Case

A 10-year-old boy with history of hepatitis 3 months before admission was referred to our hospital. At the time of admission, the total serum bilirubin were 8.3 mg/dL (6 mg/dL direct

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bilirubin), with alanine aminotransferase (ALT) 407 IU/L, aspartate aminotransferase (AST) 277 IU/L, white blood cells (WBC) 3.6×10^9 /L, Hemoglobin 12 g/dL, and Platelet 34×10^9 /L, respectively. Serologic tests for hepatitis A, B, C, EBV*, and HSV** were negative. Wilson disease was ruled out by appropriate evaluation. ANA***, ASMA****, LKM***** were negative. With possibility of autoimmune hepatitis, Prednisolone (1-2 mg/kg/day) was started. The liver function tests became normal. Following the treatment thrombocytopenia and neutropenia remained but depletion of hemoglobin count was not significant. Bone marrow aspirate and biopsy were revealed hypocellular bone marrow without malignancy evident. Prednisolone was discontinued. The patient was candidate for bone marrow transplantation and HLA***** matching. Post hepatitis aplastic anemia was diagnosed and therapy was begun with Anti thrombocytic globulin and Cyclosporine. The WBC, platelet count and hemoglobin remained more than 3.1×10^9 /L, 100×10^9 /L and 9 g/dL respectively after 6 months of treatment.

Second Case

An 11-year-old boy with hepatitis and fever was transferred to the Hospital 4 weeks after the onset of flu-like symptoms. Based on the examination, he had not chronic liver disease. Normal CBC*****, direct hyperbilirubinemia (17 mg/dL), PT***** (25), and ALT & AST (970 and 1200 IU/L respectively) were determined. Various evaluations for high-grade fever such as Malaria, Brucella, Bone Marrow Culture, ultrasound for abdominal abscess, Endocarditis, and stool culture had been taken and they were

* Epstein-Barr Virus

** Herpes Simplex Virus

*** Antinuclear Antibody

**** anti-smooth muscle antibody

***** anti-liver, kidney, muscle antibody

***** human leukocyte antigen

***** complete blood count

***** prothrombine time

negative.

Because of neutropenia and fever, antibiotic therapy was begun and fever disappeared after 10 days of treatment. The patient developed pancytopenia (hemoglobin, WBC count, and platelet count were 6.6 gr/dL, 1.3×10^3 , 31×10^3 respectively). Serologic tests for Hepatitis A, B, C, HIV*****, CMV*****, EBV, and AIH***** were negative except weakly positive ASMA. Wilson criteria were absent. Bone marrow aspiration showed hypoplastic bone marrow. Therefore, the diagnosis of HAAA was confirmed and treatment begun with ATG, Cyclosporine and Prednisolone. The blood count was within the normal range after 5 years of continuing therapy.

DISCUSSION

Aplastic anemia complicating hepatitis is a rare but well-documented phenomenon. The mechanisms leading to marrow failure remains unknown. HAAA is a severe disorder with a high mortality (85%); the responsible agent for most cases of HAAA has not been identified, although it is presumed to be viral.

HAAA is often first noted as the patient is recovering from the acute hepatic process. The aplasia commonly runs a fulminate course, and mortality is high. A relationship between hepatitis and the subsequent development of aplastic anemia has been the subject of a number of case reports; this association was emphasized by two major reviews in the 1970s.

During the 20-year period between 1967 and 1986, 5500 children (aged 2 months-14 years) with viral hepatitis were hospitalized in Thessaloniki pediatric department. In 4 children (0.07%) hepatitis was complicated with aplastic anemia. All 4 patients died. The mean duration of survival after the onset of aplastic anemia was 20.9 ± 24.8

***** human immunodeficiency Virus

***** cytomegalovirus

***** autoimmune hepatitis

weeks. The results of the serologic tests, performed in 2 patients, suggest that aplastic anemia was associated with non-A, non-B hepatitis agents.(31)

Pancytopenia with aplastic marrow has been reported with increasing frequency in association with a variety of viral illnesses, especially infectious hepatitis. Transient, mild decrease of peripheral blood elements is a common feature of hepatitis, but aplasia is a rare event. Aplasia has been reported uncommonly as a consequence of hepatitis A and B; moreover, epidemiological evidence suggests that these viruses are not of major etiologic significance in inducing marrow aplasia.(14,3), Other viral hepatitis such as hepatitis G virus (HGV) had been postulated as the etiologic agent, although in recent reports it has a limited role.(15), Also, hepatitis C virus (HCV) is infrequently observed in aplastic anemia. However, systemic searching has failed to implicate HCV in these cases.(1), Risk of aplastic anemia appears to be greatest after the hepatitis of the non-A, non-B variety.(1,2)

A number of other viruses have been implicated in the pathogenesis of marrow failure. B-19 parvovirus, the cause of fifth disease, leads to transient erythroid aplasia but is not known to induce aplastic anemia, HSV-6 has caused severe marrow aplasia subsequent to bone marrow transplantation for other disorders. HIV infection is frequently associated with varying degrees of cytopenia. EBV has been implicated in the pathogenesis of aplastic anemia.(3)

In a report of a female infant, bone marrow aplasia was reported with neonatal giant-cell hepatitis. It is proposed that bone marrow aplasia, as in the adult, may represent a complication of viral disease.(16)

Hepatitis-associated aplastic anemia is rare entity in general, but occurs in up to 28% of patients receiving liver transplantation for fulminant non-A, non-B hepatitis. Although cases have been reported in association with hepatitis A, B, and C, most appear to be due to a non-A-B-C virus.(18), Severe aplastic anemia developed in 9 of

31 patients who underwent liver transplantation for non-A, non-B hepatitis but in none of 1463 patients transplanted for other indications.(19)

In a study conducted at the Hadassah University Hospital between 1981 and 1997, seventeen of the 68 patients with aplastic anemia (25%) suffered from hepatitis, 12 males and 5 females, ages 5 to 36 years. The mean interval between onset of hepatitis and first indication of aplastic anemia was 62 days (range 14-225 days). The development of aplastic anemia was unrelated to age, sex or severity of hepatitis. Ten of the 17 patients (59%) achieved complete ALT recovery prior to the diagnosis of aplastic anemia. The survival rate after BMT* with stem cells from an HLA-matched sibling was similar to that for patients with non-hepatitis-associated aplastic anemia.(17)

Recovery from acquired aplastic anemia associated with hepatitis is rare. The extremely poor prognosis of patients with HAAA has prompted others to recommend immediate bone marrow transplantation.(20,21), Studies involving single centers have reported survival rates of patients with severe aplastic anemia of up to 90 percent after transplantation with HLA-matched bone marrow from sibling donors, with larger studies showing survival rates of 66 percent.(22,24), Unfortunately, long-term survival after transplantation of HLA-matched marrow from unrelated donors is only about half that with HLA-matched transplants from sibling donors.(25-27), Also, the combination of cyclophosphamide and ATG, and prednisone is used to reduce the risk of rejection in the patients with severe aplastic anemia and in recipients of unrelated marrow grafts.(2,28,29), In a Russian study, 16 patients with aplastic anemia whom had been detected after acute viral hepatitis received immunosuppressive therapy. The immunosuppressive therapy produced a response in 44% of the patients. Therefore aplastic anemia following acute viral hepatitis demands intensive and long term immunosuppressive therapy with antilymphocytic

* bone marrow transplantation

globulin, cyclosporin A, splenectomy (in some cases) to achieve a persistent clinicohematological remission.(30)

Bone marrow transplantation recommend for patients, who don't response to the immunosuppressive therapy.

In this study, our patients had the typical features of hepatitis-associated aplastic anemia. Both of them had aplastic anemia one and three months after acute hepatitis. Also, both of them were boys and had a complete response to immunosuppressive treatment within 6 months and 5 years, respectively. We did not identify any specific cause. There was no evidence of hepatitis A or B infection and no antibody or PCR* evidence of hepatitis C.

Our study confirms that hepatitis-associated aplastic anemia is a distinct type of aplastic anemia. The clinical features and, particularly, the response to immunosuppressive therapy strongly suggest that immune mechanisms mediate the marrow aplasia. The cause of the hepatitis is unknown, but it does not appear to be due to any of the known hepatitis viruses. In contrast to other reports, in our study the outcome was not invariably fatal and both patients responded well to immunosuppressive therapy, without exacerbation of the hepatitis.

CONCLUSION

Hepatitis-associated aplastic anemia does not appear to be caused by any of the known hepatitis viruses. We recommend immunosuppressive treatment for patients who do not have an HLA-matched related donor available for bone marrow transplantation.

References

1. Lee. A. Viral infectious hepatitis Pediatric Gastrointestinal Disease. Philadelphia; Sunders: 2004. 1170-8.
2. Sherlock S, Dooley J. Disease of the Liver and Billiary System. Black well 2002; 271-2.
3. Lee GR., et al. Wintrobe's clinical Hematology. 1999; ch.54.
4. Brown KE, Tisdale J, Barrett AJ, Dunbar CE, Young NS. Hepatitis-Associated Aplastic Anemia. *N Engl J Med* 1997; 336: 1059-64.
5. Lorenz E, Quaiser K, Panmyelopathie nach Hepatitis epidemica. *Wien Med Wochenschr* 1955; 105: 19-22.
6. Fomina LG. K voprosu obizmenenii krovetvorennia pri zabolevaniiaxh pecheni. *Sov Med* 1955; 19: 28-31.
7. Hagler L, Pastore RA, Bergin JJ, Wrensch MR. Aplastic anemia following viral hepatitis: report of two fatal cases and literature review. *Medicine* (Baltimore) 1975; 54: 139-64.
8. Bottiger LE, Westerholm B. Aplastic anaemia. III. Aplastic anaemia and infectious hepatitis. *Acta Med Scand* 1972; 192: 323-6.
9. Mary JY, Baumelou E, Guiguet M. Epidemiology of aplastic anemia in France: A prospective multicentric study. *Blood* 1990; 75: 1646-53.
10. Young NS, Issaragrasil S, Chieh CW, Takaku F. Aplastic anaemia in the Orient. *Br J Haematol* 1986; 62: 1-6.
11. Liang DC, Lin KH, Lin DT, Yang CP, Hung KL, Lin KS. Post-hepatitis aplastic anaemia in children in Taiwan, a hepatitis prevalent area. *Br J Haematol* 1990; 74: 487-91.
12. Hibbs JR, Frickhofen N, Rosenfeld SJ, Feinstone SM, Kojima S, Bacigalupo A, et al. Aplastic anemia and viral hepatitis: non-A, non-B, non-C? *JAMA* 1992; 267: 2051-4.
13. Pol S, Driss F, Devergie A, Brechot C, Berthelot P, Gluckman E. Is hepatitis C virus involved in hepatitis-associated aplastic anemia? *Ann Intern Med* 1990; 113: 435-7.
14. Gruber A, Grillner L, Norder H, Magnus L, Bjorkholm M. Severe aplastic anemia associated with seronegative community-acquired hepatitis C virus infection. *Annals of Hematology* 1993; 66: 157-9.
15. Kiem HP, Strob R, McDonald GB. Hepatitis-Associated Aplastic Anemia. *N Engl J Med* 1997; 337: 424-5.
16. Bosman C, Baldini D, Boldrini R, Gomes V, Donfrancesco A, Miano C. Aplastic anemia and neonatal giant-cell hepatitis. *Applied Pathology* 1988; 6: 49-55.
17. Safadi R, Or R, Ilan Y, Naparstek E, Nagler A, Klein A, et al. Lack of known hepatitis virus in hepatitis-associated aplastic anemia and outcome after bone marrow transplantation. *Bone Marrow Transplantation* 2001; 27: 183-90.
18. Pardi DS, Romero Y, Mertz LE, Douglas DD. Hepatitis-associated aplastic anemia and acute parvovirus B19 infection: a report of two cases and a review of the literature. *American J of Gastroenterology* 1998; 93: 468-70.
19. Tzakis AG, Ardit M, Whittington PF, Yanaga K, Esquivel C, Andrews WA, et al. Aplastic anemia complicating orthotopic liver transplantation for non-A, non-B hepatitis. *N Engl J Med* 1988; 319: 393-6.
20. Camitta BM, Nathan DG, Forman EN, Parkman R, Rapoport JM, Orellana TD. Posthepatic severe aplastic anemia-an indication for early bone marrow transplantation. *Blood*. 1974; 43: 473-83.
21. Gluckman E, Devergie A, Faille A, Bussel A, Benbunan M, Bernard J. Antilymphocyte globulin treatment in severe aplastic anemia-comparison with bone marrow

* Polymerase chain reaction

- transplantation: report of 60 cases. *Haematol Bluttransfus* 1979; 24: 171-9.
22. May WS, Sensenbrenner LL, Burns WH, Ambinder R, Carroll MP, Griffin CA, *et al.* BMT for severe aplastic anemia using cyclosporine. *Bone Marrow Transplant* 1993; 11: 459-64.
 23. Storb R, Etzioni R, Anasetti C, Appelbaum FR, Buckner CD, Bensinger W, *et al.* Cyclophosphamide combined with antithymocyte globulin in preparation for allogeneic marrow transplants in patients with aplastic anemia. *Blood* 1994; 84: 941-9.
 24. Champlin RE, Horowitz MM, van Bekkum DW, Camitta BM, Eiftenbein GE, Gale RP, *et al.* Graft failure following bone marrow transplantation for severe aplastic anemia: risk factors and treatment results. *Blood* 1989; 73: 606-13.
 25. Bradley BA, Hows JM, Gore SM, Bidwell JL, Clay T, Downie TR, *et al.* Current status of unrelated-donor bone marrow transplantation: the International Marrow Unrelated Search and Transplant (IMUST) Study. *Clin Transpl* 1992; 91-107.
 26. Kernan NA, Bartsch G, Ash RC, Beatty PG, Champlin R, Filipovich A, *et al.* Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. *N Engl J Med* 1993; 328: 593-602.
 27. Margolis D, Camitta B, Pietryga D, Keever-Taylor C, Baxter-Lowe LA, Pierce K, *et al.* Unrelated donor bone marrow transplantation to treat severe aplastic anaemia in children and young adults. *Br J Haematol* 1996; 94: 65-72.
 28. Matloub YH, Bostrom B, Golembe B, Priest J, Ramsay NK. Antithymocyte globulin, cyclosporine, and prednisone for the treatment of severe aplastic anemia in children. A pilot study. *American Journal of Pediatric Hematology-Oncology* 1994; 16: 104-6.
 29. Brown KE, Tisdale J, Barrett AJ, Dunbar CE, Young NS. Hepatitis-Associated Aplastic Anemia. *N Engl J Med* 1997; 336: 1059-64.
 30. Mikhailova EA, Iadrikhinskaia VN, Savchenko VG. Aplastic Anemia and viral hepatitis (posthepatitis aplastic anemia). *Terapevticheskii Arkhiv* 1999; 71: 64-9.
 31. Pikiş A, Kavalıoğlu J, Manios S. Incidence of aplastic anemia in viral hepatitis in children. 1988; 20:109-10.