

## HEPATITIS-ASSOCIATED APLASTIC ANEMIA

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**ABSTRACT**

**Background** Hepatitis-associated aplastic anemia is a variant of aplastic anemia in which aplastic anemia follows an acute attack of hepatitis. The aplastic anemia, however, is often fatal if untreated. To characterize the illness, investigate the role of hepatitis viruses, and assess the response to immunosuppressive treatment, we studied patients with the syndrome who were referred to the National Institutes of Health (NIH).

**Methods** Standard hematologic and biochemical tests and measurements of bone marrow cellularity were used to monitor the patients' response to treatment. Serum was assayed for antibodies and antigens related to hepatitis A, B, and C viruses and for the RNA of hepatitis C and GB virus C by the polymerase chain reaction. All patients were treated with antithymocyte globulin and cyclosporine.

**Results** Ten patients with hepatitis-associated aplastic anemia were referred to the NIH between 1990 and 1996; all had the typical features of this syndrome. There was evidence of activated CD8 T lymphocytes in the blood. Serologic tests for hepatitis A, B, and C viruses were negative; RNA of hepatitis C virus was undetectable in all patients, but RNA of GB virus C was detected in three patients. Seven of the patients responded to intensive immunosuppressive treatment; the three who did not respond all died within one year of treatment, two from complications of stem-cell or marrow transplantation.

**Conclusions** The hepatitis of the 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. Several features of the syndrome suggest that it is mediated by immunopathologic mechanisms. (N Engl J Med 1997;336:1059-64.)

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**H**EPATITIS-ASSOCIATED aplastic anemia was first described in 2 case histories in 1955,<sup>1,2</sup> and by 1975 more than 200 cases had been reported.<sup>3</sup> As a syndrome of bone marrow failure, hepatitis-associated aplastic anemia is not uncommon, with hepatitis documented in 2 to 5 percent of cases of aplastic anemia in the West<sup>4,5</sup> and 4 to 10 percent in the Far East.<sup>6</sup> 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.<sup>7</sup> Hepatitis-

associated aplastic anemia most often affects adolescent boys and young men,<sup>3</sup> who present with severe pancytopenia two to three months after an episode of acute hepatitis. The marrow failure can be precipitous and severe and is usually fatal if untreated.<sup>3</sup> There is no known association with blood transfusions, drugs, or toxins, and most patients have been seronegative for hepatitis A, B, and C.<sup>8,9</sup>

Aplastic anemia is also not uncommon after orthotopic liver transplantation performed for fulminant non-A, non-B hepatitis in young patients. In a study conducted at the University of Pittsburgh, aplastic anemia developed in 28 percent of such patients (9 of 32), as compared with none of 1463 patients undergoing liver transplantation for other causes.<sup>10</sup> In a study at the University of Nebraska, aplastic anemia developed in 33 percent of children (6 of 18) who required liver transplantation for fulminant non-A, non-B, non-C hepatitis.<sup>11</sup> The cause of fulminant seronegative hepatitis is unknown.<sup>12</sup>

We performed a retrospective analysis of patients with hepatitis-associated aplastic anemia who were referred to the Clinical Center at the National Institutes of Health (NIH).

**METHODS****Patients**

Between June 1990 and June 1996, 10 patients were referred to the NIH for the evaluation of severe aplastic anemia that had developed within three months after documented hepatitis. Severe aplastic anemia was defined as pancytopenia with at least two of the following abnormalities: an absolute neutrophil count of less than 500 per cubic millimeter, a platelet count of less than 20,000 per cubic millimeter, and a reticulocyte count of less than 60,000 per cubic millimeter, in association with a bone marrow cellularity of less than 30 percent. Hepatitis was defined as an increase in serum aminotransferase levels to at least three times the upper limit of the normal range (normal range for alanine aminotransferase, 6 to 41 U per liter; normal range for aspartate aminotransferase, 9 to 34 U per liter). A complete response was defined as normal or near-normal blood counts within a year after the initiation of therapy (hemoglobin concentration, >10 g per deciliter; absolute neutrophil count, >1000 per cubic millimeter; and platelet count, >100,000 per cubic millimeter).

All the patients received intensive immunosuppression with equine antithymocyte globulin (Upjohn, Kalamazoo, Mich.) at a dose of 40 mg per kilogram of body weight per day intravenously for four days combined with a six-month course of cyclosporine

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(12 to 15 mg per kilogram per day orally, with adjustment of the dose to maintain a blood level between 200 and 400 ng per milliliter).<sup>13</sup> Beginning in 1995, cyclosporine treatment was continued at tapering doses for a further 26-week period. Patient 9 followed this regimen before his referral, and at the NIH he received cladribine (2-chlorodeoxyadenosine), given as an intravenous infusion of 0.1 mg per kilogram per day for seven days, as experimental treatment for refractory aplastic anemia. The protocols were approved by the institutional review board of the National Heart, Lung, and Blood Institute, and all patients gave written informed consent before their participation. The following is a representative case history.

Patient 7, a 15-year-old student from Colorado, presented in July 1995 with nausea and abdominal pain followed 10 days later by jaundice (bilirubin level, 14.4 mg per deciliter [246  $\mu$ mol per liter]; aspartate aminotransferase level, 1777 U per liter; and alanine aminotransferase level, 3372 U per liter). One month later liver function had improved slightly, but cytopenia had developed (hemoglobin concentration, 12.1 g per deciliter; leukocyte count, 1400 per cubic millimeter; neutrophil count, 710 per cubic millimeter; and platelet count, 44,000 per cubic millimeter). On admission to the NIH in late August, the patient's liver-enzyme levels were still abnormal (aspartate aminotransferase level, 1892 U per liter; and alanine aminotransferase level, 1956 U per liter), and he had pancytopenia (hemoglobin concentration, 9.3 g per deciliter; leukocyte count, 600 per cubic millimeter; neutrophil count, 468 per cubic millimeter; and platelet count, 30,000 per cubic millimeter). An examination of bone marrow confirmed the presence of aplastic anemia, and treatment with antithymocyte globulin, cyclosporine, and granulocyte colony-stimulating factor was started. Within a month liver function was normal, and by three months the hematologic values had improved (hemoglobin concentration, 11.1 g per deciliter; leukocyte count, 2700 per cubic millimeter; neutrophil count, 1500 per cubic millimeter; and platelet count, 117,000 per cubic millimeter). In August 1996 his bone marrow was slightly hypocellular for his age but showed normal trilineage maturation, the hemoglobin concentration was 13.2 g per deciliter, the leukocyte count was 3300 per cubic millimeter, the neutrophil count was 2100 per cubic millimeter, and the platelet count was 134,000 per cubic millimeter. The patient remains well 18 months after the initiation of treatment. There is no evidence of paroxysmal nocturnal hemoglobinuria or myelodysplastic syndrome.

### Immunologic Testing

Peripheral-blood mononuclear cells were examined by flow cytometry to quantitate the number and phenotype of B and T lymphocytes with directly conjugated monoclonal antibodies against CD2, CD3, CD4, CD8, CD19, and HLA-DR (Becton Dickinson, Mountain View, Calif.).

### Serologic Analysis

Standard commercial assays were used to test serum samples for hepatitis A antibody (IgM and IgG), hepatitis B surface antigen and antibody, hepatitis B core antibody, and hepatitis C antibody. In addition, hepatitis C virus (HCV) RNA and GB virus C (GBV-C) RNA<sup>14,15</sup> were tested for by reverse transcription followed by the polymerase chain reaction (PCR) as previously described.<sup>16,17</sup>

## RESULTS

### Clinical Features

On admission to the NIH all 10 patients had evidence of severe aplastic anemia, as indicated by blood counts and bone marrow findings. All but one were children or young adults (<30 years of age), and seven were male (Table 1). The clinical features were

similar in all cases; none of the patients had a history of exposure to toxins or chemicals, blood transfusion, or parenteral treatment of any kind before the onset of illness. All had markedly elevated liver-enzyme levels, generally with aminotransferase levels in the thousands of units per liter, and the interval between hepatitis and the onset of aplasia was short (less than one week to seven weeks). In seven patients without pancytopenia at presentation, liver function appeared to be improving at the time of the onset of aplasia.

### Immunologic Features

Flow-cytometric analysis showed abnormalities of the CD4 and CD8 counts in all patients. The mean ( $\pm$ SD) absolute counts were  $99.5 \pm 182$  CD4 cells per cubic millimeter (range, <4 to 602),  $140 \pm 157$  CD8 cells per cubic millimeter (range, <7 to 545), and  $40 \pm 36$  HLA-DR-positive CD8 cells per cubic millimeter (range, <1 to 101). The percentage of CD4 cells was below the normal range in all patients; in nine patients the percentage of CD8 T cells was above normal. All patients had an increased percentage of HLA-DR-positive CD8 cells, indicating activation of cytotoxic T cells (Fig. 1).

### Response to Immunosuppressive Treatment

All the patients were treated with a four-day course of intravenous antithymocyte globulin and a six-month course of oral cyclosporine.<sup>13</sup> Liver-enzyme levels returned to normal within one month after treatment was begun in all patients except Patient 9, whose aminotransferase levels fell (but not to normal) two weeks after antithymocyte globulin was given and then rose again. The aminotransferase levels returned to normal in Patient 9 after treatment with cladribine. Hematologic improvement after antithymocyte globulin treatment was slower: in five patients the blood counts returned toward normal within six months after treatment was begun (Fig. 2), and two other patients were transfusion-independent at nine months. Of the three patients who did not respond to treatment with antithymocyte globulin, Patient 2 was subsequently shown to have monosomy 7, and Patient 8 was critically ill before starting therapy and underwent stem-cell transplantation within one month after treatment was begun. Patient 9 did not respond to two courses of immunosuppression (Table 2).

Patient 6 responded to the immunosuppressive treatment, but one year after receiving antithymocyte globulin therapy and one month after the discontinuation of cyclosporine, his aminotransferase levels rose again; two months later cytopenia developed (neutrophil count, 312 per cubic millimeter; platelet count, 9000 per cubic millimeter) with an aplastic marrow. He received a second course of antithymocyte globulin and cyclosporine, with a full hepatic and

**TABLE 1.** CLINICAL CHARACTERISTICS OF PATIENTS WITH HEPATITIS-ASSOCIATED APLASTIC ANEMIA.\*

PATIENT No.	AGE (YR)/SEX	OCCUPATION	PEAK AST	PEAK ALT	INTERVAL BETWEEN HEPATITIS AND ANEMIA	LOWEST ANC
1	16/M	Student	4517	3154	5	78
2	11/M	Student	1131	527	6	450
3	8/F	Student	2527	1727	7	350
4	24/M	Dental student	1305	1296	6	200
5	27/M	Graduate student	465	978	<1	180
6	27/M	Police officer	1236	2500	7	312
7	15/M	Student	2228	2389	4	0
8	40/F	Lawyer	1011	1440	3	0
9	18/M	Oil-field worker	1590	752	<1	0
10	28/F	Homemaker	664	2233	<1	350

\*AST denotes aspartate aminotransferase, ALT alanine aminotransferase, and ANC absolute neutrophil count.

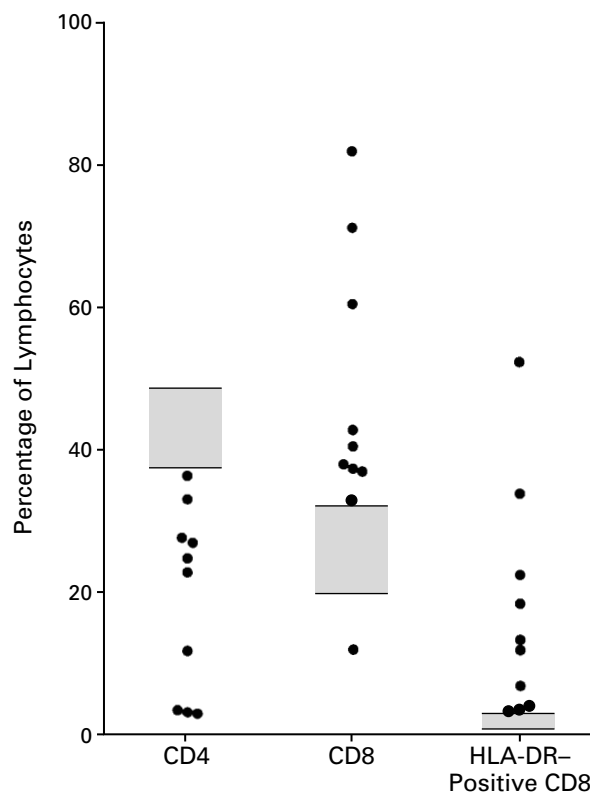
hematologic response (Table 2). None of the other patients have relapsed to date, nor has paroxysmal nocturnal hemoglobinuria or myelodysplasia developed in any of them.

#### Virologic Assays

Patient 10 had evidence of previous infection with hepatitis B (tests were positive for hepatitis B surface and core antibody and negative for hepatitis B surface antigen). In the other nine patients serologic tests for hepatitis A, hepatitis B, and HCV were all negative, confirming that none had evidence of recent or current infection with any of these viruses. The reverse-transcription PCR for HCV RNA was negative in all patients but was positive for GBV-C RNA in three patients (Patients 4, 5, and 9) at the time of admission to the NIH. All three of these patients had received multiple blood transfusions before testing as part of their treatment (16, 20, and 35 units, respectively). Serum was available from 12 of the 16 units donated to Patient 4, and one of these samples was found to contain GBV-C.

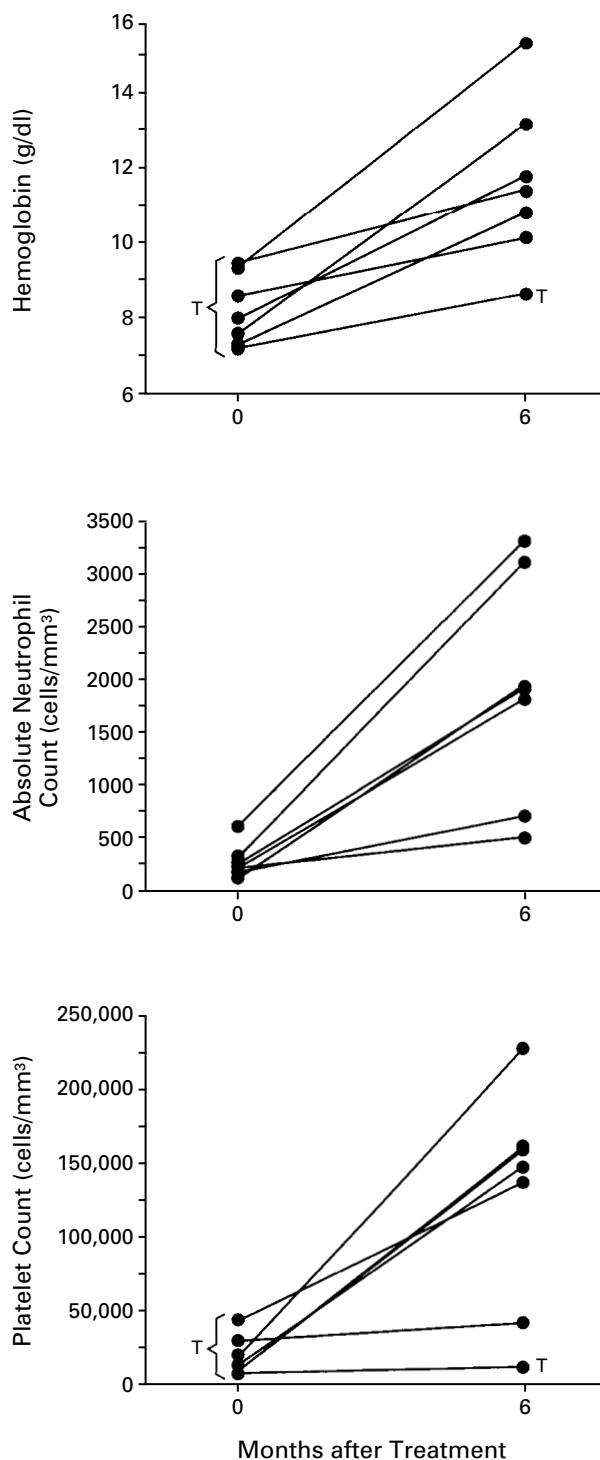
#### DISCUSSION

Our patients had the typical features of hepatitis-associated aplastic anemia. All had acute hepatitis that was followed within two months by aplastic anemia or pancytopenia.<sup>3</sup> Most were young males,<sup>3</sup> and 7 of the 10 patients had a complete response to immunosuppressive treatment within one year. The hepatitis was clinically indistinguishable from a typical viral hepatitis, but no specific cause could be identified: there was no evidence of active or recent hepatitis A or B infection and no antibody or PCR evidence



**Figure 1.** Flow-Cytometric Analysis of Peripheral-Blood Lymphocytes from Patients before Treatment with Antithymocyte Globulin and Cyclosporine.

Shaded areas indicate normal ranges.



**Figure 2.** Hematologic Values before and Six Months after Treatment with Antithymocyte Globulin and Cyclosporine Was Begun.

Only values for the seven patients who responded to treatment with antithymocyte globulin are shown. T denotes transfusion.

of hepatitis C. GBV-C RNA was detected in three patients, but they had received multiple blood transfusions; in one patient serum from one of the transfused units contained the virus. None of the remaining patients had detectable GBV-C viremia, even early in the course of their illness. These negative results were obtained with three different assays for viral sequences from the 5' untranslated region and polymerase regions of the viral genome (data not shown). Thus, GBV-C does not appear to be the etiologic agent of hepatitis-associated aplastic anemia.

Our results, especially the response to immunosuppressive treatment, suggest that the liver and marrow abnormalities in hepatitis-associated aplastic anemia are immune-mediated. At presentation, all patients had activated CD8 cells in the blood, in several cases before the transfusion of any blood products. Levels of activated CD8 cells fell with treatment in all patients, except Patient 9, who had no response to immunosuppressive treatment. In Patient 6, the number of activated CD8 cells declined, but not to normal, despite one year of treatment with cyclosporine. After immunosuppressive therapy was stopped the number of activated CD8 cells again rose, this time in parallel with an elevation in serum aminotransferase levels that heralded a relapse. With retreatment the levels again declined.

In this study, activated lymphocytes stained brightly with a fluorescent anti-CD8 antibody, a reaction that is consistent with the presence of a T-cell phenotype, but we cannot rule out the possibility that this population also included natural killer cells. We did not determine whether the activated CD8 cells could inhibit or kill hepatic or hematopoietic target cells, but previous studies have shown that lymphocytes from patients with aplastic anemia suppress the *in vitro* proliferation of hematopoietic progenitor cells from patients and normal donors.<sup>18</sup> Moreover, in aplastic anemia activated cytotoxic lymphocytes localize in the bone marrow,<sup>19,20</sup> and there are increased levels of interferon gamma, a lymphokine product of activated CD8 and CD4 T cells, in the bone marrow.<sup>21,22</sup> T-cell activation is common in viral infection, and cytotoxic T cells are thought to mediate the liver inflammation in hepatitis B and hepatitis C infection,<sup>23,24</sup> but lymphocytes do not appear to be activated in uncomplicated seronegative hepatitis.<sup>25</sup> The rapid improvement of hepatitis with immunosuppressive treatment in our patients is consistent with an immune-mediated pathophysiology.

The extremely poor prognosis of patients with hepatitis-associated aplastic anemia has prompted others to recommend immediate bone marrow transplantation.<sup>26,27</sup> 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,

TABLE 2. RESPONSE OF PATIENTS TO IMMUNOSUPPRESSIVE THERAPY.\*

PATIENT NO.	TIME BETWEEN ONSET OF PANCYTOPENIA AND TREATMENT	THERAPY (DATE)	TIME FROM INITIATION OF THERAPY TO ANC >500/mm <sup>3</sup>	TIME FROM INITIATION OF THERAPY TO INDEPENDENCE FROM TRANSFUSION	RESPONSE WITHIN 1 YR AFTER ATG TREATMENT†
1	4 wk	ATG, CSA (10/90)	7 days	3 mo	Complete response
2	6 wk	ATG, CSA (1/91)	—	—	Only aminotransferase levels normalized
	9 mo	BMT	—	—	Died of venoocclusive disease 1 mo after BMT
3	5 mo	ATG, CSA (8/91)	—‡	—	Complete response
4	7 wk	ATG, CSA (3/95)	6 mo	9 mo	Complete response
5	4 mo	ATG, CSA (6/95)	3 mo	6 mo	Complete response
6	18 days	ATG, CSA (9/95)	24 days	1 mo	Complete response, relapse
	14 mo	ATG, CSA	24 days	2 mo	Complete response
7	11 days	ATG, CSA (8/95)	37 days	3 mo	Complete response
8	16 days	ATG, CSA (10/95)	—	—	Only aminotransferase levels normalized
	1.5 mo	PBSCT	10 days	—	Died of multiorgan failure 53 days after transplantation
9	5 wk	ATG, CSA (12/95)	—	—	No response
	3 mo	Cladribine	—	—	Only aminotransferase levels normalized; died of fungal infection 4 mo after treatment begun
10	10 days	ATG, CSA (4/96)	35 days	2 mo	Complete response

\*ANC denotes absolute neutrophil count, ATG antithymocyte globulin, CSA cyclosporine, BMT bone marrow transplantation, and PBSCT peripheral-blood stem-cell transplantation.

†A complete response was defined as normal or near-normal blood counts within a year after the initiation of therapy (hemoglobin concentration, >10 g per deciliter; absolute neutrophil count, >1000 per cubic millimeter; and platelet count, >100,000 per cubic millimeter).

‡This patient's absolute neutrophil count never dropped below 500 cells per cubic millimeter, and she received only platelet transfusions before antithymocyte globulin therapy was begun.

with larger studies showing survival rates of 66 percent.<sup>28-30</sup> In registries that included more than 50 patients with post-hepatitis aplasia, the hepatitis did not affect the overall rates of graft failure,<sup>30</sup> the rate of acute or chronic graft-versus-host disease,<sup>31</sup> or long-term survival.<sup>32</sup> These results justify the use of bone marrow transplantation in the minority of young patients for whom an HLA-identical sibling is available.<sup>28-30,32,33</sup> 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.<sup>31,34,35</sup> Our results with antithymocyte globulin and cyclosporine are equivalent to those in patients with uncomplicated severe aplastic anemia who received such treatment and to the results with HLA-identical marrow transplantation for aplastic anemia regard-

less of the cause.<sup>7,11,36,37</sup> Treatment with antithymocyte globulin and cyclosporine can be safely initiated immediately after diagnosis, allowing time to search for an alternative donor in patients without an HLA-identical sibling.

Our study confirms that hepatitis-associated aplastic anemia is a distinct type of aplastic anemia with a stereotypical pattern. The clinical features and, particularly, the response to immunosuppressive therapy strongly suggest that immunologic 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 previous reports, in our study the outcome was not invariably fatal and most patients responded well to immunosuppressive therapy, without exacerbation of the hepatitis.

We are indebted to Stacie Anderson, Martha Kirby, and Susan Wong for sample analysis, and to Mary Caples, Janice Kimball, and the 2 West nursing staff at the NIH.

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