Published in final edited form as:
N Engl J Med. 1988 August 18; 319(7): 393–396. doi:10.1056/NEJM198808183190702.

APLASTIC ANEMIA COMPLICATING ORTHOTOPIC LIVER TRANSPLANTATION FOR NON-A, NON-B HEPATITIS

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Abstract

Aplastic anemia developed in 9 of 32 patients (28 percent) undergoing orthotopic liver transplantation for acute non-A, non-B hepatitis, at one to seven weeks after the procedure. No patient previously had evidence of hematologic dysfunction or conditions known to be associated with aplastic anemia. No other cases of aplastic anemia were identified among 1463 patients undergoing liver transplantation for all other indications at the four centers participating in the study (chi-square = 415, P<0.001; 95 percent confidence interval for the incidence of aplastic anemia after transplantation for non-A, non-B hepatitis, 13 to 44 percent, vs. 0.00 to 0.13 percent for all other indications).

The operative and postoperative treatment of these patients was not otherwise different, indicating that the aplastic anemia was a complication of the hepatitis, not of the transplantation procedure. Four of the nine patients died of complications due to infections. Three of the surviving patients have been followed for less than six months, one for one year, and one for two years. The two patients followed the longest have recovered marrow function to an appreciable degree, and two of the others have evidence of early recovery.

We conclude that patients undergoing orthotopic liver transplantation for non-A, non-B hepatitis are at a high risk for the development of aplastic anemia.

Liver failure after severe acute or subacute hepatitis is an accepted indication for orthotopic liver transplantation. A recent analysis of 29 patients with acute liver failure demonstrated that the odds in favor of survival were greatly increased by transplantation, and the causes of treatment failure did not appear to be different from those in patients who underwent transplantation for other reasons.[1–3] We present clinical data on nine patients who had aplastic anemia after transplantation, a complication that may be unique to patients with acute non-A, non-B viral hepatitis.

METHODS

The records of the four cooperating liver-transplant centers (the University of Pittsburgh, the University of Chicago, the University of Texas–Southwestern, and the University of Minnesota) were searched to identify patients in whom aplastic anemia had been diagnosed

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after they had received a liver transplant. Nine such patients were identified, and investigators at each institution comprehensively reviewed the hospital charts. Computerized data bases provided information on the total population of 1495 patients who had undergone liver transplantation in these four centers. The case of one patient has been briefly reported elsewhere.[4]

Patients underwent transplantation because of evidence of severe impairment of hepatic function, from which they were not expected to recover. In these patients, acute hepatitis was defined as leading to hepatic failure within 8 weeks, and subacute hepatitis leading to hepatic failure within 8 to 28 weeks.[1]

A thorough medical history, which included reference to chronic liver disease, autoimmune disease, and exposure to hepatitis, drugs, or toxins, was available in each case. Serologic testing for hepatitis A (antibody to hepatitis A virus IgM), hepatitis B (hepatitis B surface antigen, antibody to hepatitis B surface antigen, core antibody IgM, hepatitis B e antigen, and e antibody), Epstein–Barr virus, cytomegalovirus, and herpes simplex virus was performed in all cases. Wilson's disease was diagnosed if low serum concentrations of ceruloplasmin and characteristic clinical findings were present. Non-A, non-B hepatitis was diagnosed if other causes of acute or subacute liver failure could be excluded.

Aplastic anemia was defined as a profound and protracted reduction in the concentration of blood elements derived from the bone marrow, which required transfusion therapy and was related to marked hypoplasia or aplasia of the bone marrow.[5,6] Marrow samples were cultured for bacterial, fungal, and viral pathogens.

RESULTS

Table 1 shows the characteristics of the nine patients in whom aplastic anemia developed. In each, the indication for transplantation was non-A, non-B hepatitis. All were in good health before the onset of hepatitis. None had a history of exposure to toxins, and none were receiving medication at the time of the onset of hepatitis.

The source of hepatitis was not evident in any of these patients. None had a history of exposure to hepatitis. Among the patients with non-A, non-B hepatitis who did not become anemic, several of the adult patients did have percutaneous exposure, and the sibling of one child subsequently had self-limited acute hepatitis. One patient (No. 3) had an earlier episode of hepatitis without serologic markers, 11 months before the episode that led to transplantation.

The histopathological appearance of the liver specimens was consistent with severe viral hepatitis[7]; massive necrosis was observed in eight specimens, and submassive necrosis in one.

The hematologic values shown in Table 1 were those last obtained before transplantation. None of the patients had had prior episodes of prolonged bone marrow dysfunction or any condition associated with aplastic anemia. None had had evidence of aplastic anemia before the procedure, although all had received infusions of blood products before surgery. The absolute neutrophil count determined before transplantation ranged from 1240 to 5230 per cubic millimeter, and the hematocrit from 28.1 to 37.3 percent. Thrombocytopenia occurred in three patients; in two patients (No. 2 and 6) it could not be explained, and in the third (Patient 9) it was associated with a course of acyclovir given because of exposure to chickenpox. A bone marrow examination performed before transplantation showed normal results in one patient (No. 8), and an examination performed five days after transplantation

because of transient thrombocytopenia demonstrated increased megakaryocytes in another patient (No. 6) (Table 2).

The onset of aplastic anemia occurred 3 to 22 weeks after the onset of hepatitis and 1 to 7 weeks after transplantation (Table 2). Normal blood counts had been documented in all patients in the interval after transplantation. These patients received various medications before the onset of aplastic anemia, and the majority had received drugs with potential toxicity to bone marrow. However, the pattern of administration and the variety of drugs that they received were in no way unusual for transplant recipients in these centers. Bone marrow cultures — first obtained after the onset of aplastic anemia in seven patients, before transplantation in one, and in the interval between transplantation and the onset of aplastic anemia in one — were negative in all cases.

The treatment of the patients and their outcomes are shown in Table 3. The general strategy employed by all the centers was to withhold any medications that might have contributed to bone marrow dysfunction. Immunosuppression was discontinued or reduced — in principle, to reduce the risk of infection. Three patients (No. 1, 2, and 6) had allograft rejection, which necessitated repeat transplantation in one. Five patients received preparations of antibodies directed against T cells: two patients (No. 1 and 2) for the treatment of rejection, and three (No. 6, 7, and 9) as therapy for aplastic anemia.[8]

Three patients died of systemic fungal infection (two of aspergillus and one of candida). Hepatitis developed in the allograft of one patient (No.3); he received a second transplant, which failed to function, and died while receiving a third.

Five patients are alive at this writing. Patient 1 received four transplants. The first failed because of primary nonfunction, and the second and third because of graft rejection. The patient is alive and has normal peripheral-blood counts 24 months after receiving the fourth transplant. Patient 2, at 12 months after transplantation, has had partial recovery, with a peripheral-blood leukocyte count of 2000 and a platelet count of 20,000. He requires packed red cells and platelet transfusion therapy. Patients 4, 5, and 7 are alive after short periods of follow-up.

Table 4 shows the total experience of the participating centers with respect to the occurrence of aplastic anemia after liver transplantation. Aplastic anemia has occurred only after transplantation for non-A, non-B hepatitis, with a frequency of 28 percent. The probability that this observation is due to chance is minute (chi-square = 415, $P<0.001$). The 95 percent confidence interval for the frequency of occurrence of aplastic anemia after liver transplantation for non-A, non-B hepatitis is 13 to 44 percent, as opposed to 0.00 to 0.13 percent for all other indications, assuming the occurrence of half a case in order to do the computation.[9]

DISCUSSION

We found an extremely high frequency of occurrence (28 percent) of aplastic anemia after liver transplantation was performed for the indication of acute non-A, non-B hepatitis. This frequency is in contrast to the absence of this complication among the 1463 patients in the four cooperating centers who received liver transplants for all other indications, the frequency of 0.1 to 0.2 percent reported among patients with acute viral hepatitis who did not undergo transplantation,[10–12] and the incidence of 2 to 5 per million per year in the general population.[5,6]

Non-A, non-B hepatitis is the most frequently diagnosed cause of acute hepatic failure due to hepatitis in our centers, accounting for 58 percent of cases. (As Table 4 shows, most cases

of liver failure are not due to hepatitis.) Although several patients in the series had percutaneous exposure to hepatitis — through a transfusion, for example, or a needle stick — none of those who had aplastic anemia did. Sporadic non-A, non-B hepatitis remains a poorly defined entity, diagnosed when the patient appears to have viral hepatitis and serologic testing is negative for known agents. It is necessarily a diagnosis of exclusion, which requires an exhaustive search for other causes.[13] Non-A, non-B hepatitis is not rare, and seems to be more severe than hepatitis A or B. In one series, it accounted for 25 percent of the cases of fulminant viral hepatitis in which Grade IV encephalopathy developed among 453 patients with acute hepatic failure.[14] In other series, it was the diagnosis in 26 of 31 children with fulminant hepatitis[15] and in 32 of 73 young adults with fulminant viral hepatitis.[16] Its mortality rate is the highest among the rates for all causes of acute liver failure, which accounts for its frequency among patients referred to our centers for transplantation.

In our experience, the only patients in whom aplastic anemia developed after liver transplantation had sporadic non-A, non-B hepatitis. Few data have been reported on the occurrence of aplastic anemia among patients with non-A, non-B hepatitis and acute hepatic failure, perhaps because few patients survive long enough for this complication to develop. Although aplastic anemia is a complication in fewer than 2 per 1000 cases of typical non-A, non-B hepatitis,[17–19] 13.4 percent of cases of acquired aplastic anemia were preceded by non-A, non-B hepatitis in one large series.[20] In another series, of 31 children with fulminant hepatic failure, 2 had aplastic anemia and 2 others had prolonged thrombocytopenia; all these patients had sporadic non-A, non-B hepatitis.[15] The frequency of the occurrence of aplastic anemia in our series is higher than in any previous report. It seems possible that successful transplantation simply permitted the frequent expression of aplastic anemia, which was precluded by a death rate that approached 90 percent in other series.[21] Furthermore, it can be concluded that aplastic anemia is not a complication of liver failure. It was not a complication of the course in other patients with equal degrees of hepatic compromise, and in the majority of patients described here, liver function was normal when aplastic anemia became evident.

We could not discern any differences in the technique of transplantation, the drugs used in the postoperative period, or the types or severity of complications that distinguish these patients.

The high mortality rate ascribed to hepatitis-associated aplastic anemia[5,6,11,20] has not been observed in our patients, but the follow-up period has been short. With longer observation, a better assessment can be made of the effect of this complication on survival and the need for intervention with therapies such as bone marrow transplantation.

REFERENCES

1. Peleman RR, Gavaler JS, Van Thiel DH, et al. Orthotopic liver transplantation for acute and subacute hepatic failure in adults. Hepatology 1987;7:484–489. [PubMed: 3552924]
2. Gartner JC Jr, Zitelli BJ, Malatack JJ, Shaw BW, Iwatsuki S, Starzl TE. Orthotopic liver transplantation in children: two-year experience with 47 patients. Pediatrics 1984;74:140–145. [PubMed: 6377219]
3. Cuervas-Mons V, Martinez AJ, Dekker A, Starzl TE, Van Thiel DH. Adult liver transplantation: an analysis of the early causes of death in 40 consecutive cases. Hepatology 1986;6:495–501. [PubMed: 3519418]
4. Stock PG, Steiner ME, Freese D, Sharp H, Ascher NL. Hepatitis-associated aplastic anemia after liver transplantation. Transplantation 1987;43:595–597. [PubMed: 3107175]
5. Camitta BM, Storb R, Thomas ED. Aplastic anemia: pathogenesis, diagnosis, treatment, and prognosis. N Engl J Med 1982;306:645–652. [PubMed: 7035946]

6. Idem. Aplastic anemia: pathogenesis, diagnosis, treatment, and prognosis. N Engl J Med 1982;306:712–718. [PubMed: 7038485]
7. Bianchi, L.; Zimmerli-Ning, M.; Gudat, F. Viral hepatitis. In: MacSween, RN.; Anthony, PP.; Scheuer, PJ., editors. Pathology of the liver. Edinburgh: Churchill Livingstone; 1979. p. 164-191.
8. Champlin R, Ho W, Gale RP. Antithymocyte globulin treatment in patients with aplastic anemia: a prospective randomized trial. N Engl J Med 1983;308:113–118. [PubMed: 6336819]
9. Fleiss, J. Statistical methods for rates and proportions. 2nd ed.. New York: John Wiley; 1981. p. 176
10. Ajlouni K, Doeblin TD. The syndrome of hepatitis and aplastic anaemia. Br J Haematol 1974;27:345–355. [PubMed: 4843677]
11. Hagler L, Pastore RA, Bergin JJ. Aplastic anemia following viral hepatitis: report of two fatal cases and literature review. Medicine (Baltimore) 1975;54:139–164. [PubMed: 1117835]
12. Losowsky MS. The clinical course of viral hepatitis. Clin Gastroenterol 1980;9:3–21. [PubMed: 6105031]
13. Dienstag JL. Non-A, non-B hepatitis. I. Recognition, epidemiology, and clinical features. Gastroenterology 1983;85:439–462. [PubMed: 6305760]
14. Williams R, Gimson AES. An assessment of orthotopic liver transplantation in acute liver failure. Hepatology 1984;4 Suppl:22S–24S. [PubMed: 6363256]
15. Psacharopoulos HT, Mowat AP, Davies M, Portmann B, Silk DBA, Williams R. Fulminant hepatic failure in childhood: an analysis of 31 cases. Arch Dis Child 1980;55:252–258. [PubMed: 7416773]
16. Gimson AES, White YS, Eddleston ALWF, Williams R. Clinical and prognostic differences in fulminant hepatitis type A, B and non-A non-B. Gut 1983;24:1194–1198. [PubMed: 6416935]
17. Cargnel A, Vigano P, Davoli C, Morelli R, Perna MC, Mariscotti C. Sporadic acute non-A non-B hepatitis complicated by aplastic anemia. Am J Gastroenterol 1983;78:245–247. [PubMed: 6404160]
18. Sandberg T, Lindquist O, Norkrans G. Fatal aplastic anaemia associated with non-A, non-B hepatitis. Scand J Infect Dis 1984;16:403–404. [PubMed: 6442008]
19. Perrillo RP, Pohl DA, Roodman ST, Tsai CC. Acute non-A, non-B hepatitis with serum sickness-like syndrome and aplastic anemia. JAMA 1981;245:494–496. [PubMed: 6450290]
20. Zeldis JB, Dienstag JL, Gale RP. Aplastic anemia and non-A, non-B hepatitis. Am J Med 1983;74:64–68. [PubMed: 6295145]
21. O'Grady JG, Gimson AES, O'Brien CJ, Pucknell A, Hughes RD, Williams R. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. Gastroenterology 1988;94:1186–1192. [PubMed: 3280388]

Table 1

Clinical Characteristics of Patients with Aplastic Anemia after Liver Transplantation for Non-A, Non-B Hepatitis.

PATIENT NO.*	AGE/ RACE/ SEX	TIME FROM HEPATITIS TO TRANSPLANT	COMA GRADE	BILIRUBIN	SERUM ALT†	PRO-THROMBIN TIME	HEMA-TOCRIT	WHITE CELLS	NEUTRO-PHILS‡	PLATE-LETS
		weeks			*μmol/liter*	*U/liter*	*sec*	*%*	*per cubic mm*	*×10³/mm³*
1 (UP)	10/W/M	4	III	633	426	23.1	37.3	6,700	5,230	124
2 (UP)	7/W/F	19	I	342	249	14.6	28.8	2,300	1,240	18
3 (UP)	20/W/M	4	III	756	449	19.8	29.6	2,900	2,490	130
4 (UP)	3/W/M	3	III	653	88	41.6	31.3	4,600	3,170	128
5 (UP)	14/W/M	4	I	426	530	63.0	36.6	4,100	2,624	192
6 (UC)	5/B/M	3	III	513	2,685	65.0	35.0	7,200	2,880	57
7 (UC)	14/B/F	4	II	608	535	20.3	35.0	6,400	3,700	372
8 (UT)	4/W/M	2	III	656	390	36.0	28.1	4,100	3,610	115
9 (UM)	7/B/M	9	III	547	361	28.0	29.8	11,300	1,800	114

*UP denotes University of Pittsburgh, UC University of Chicago, UT University of Texas, and UM University of Minnesota.

†Alanine aminotransferase; to convert to microkatals per liter, multiply by 0.01667.

‡Absolute neutrophil count (<800 = low).

Table 2

Clinical Data Related to Aplastic Anemia.

PATIENT NO.	ONSET OF ANEMIA		HEMA-TOCRIT	WHITE CELLS*	NEUTRO-PHILS†	RETICU-LOCYTES†	PLATE-LETS*	BONE MARROW§	MEDICATIONS BEFORE APLASTIC ANEMIA
	FROM HEPATITIS	FROM TRANSPLANT							
	weeks		*%*	*per cubic mm*		*%*	*×10³/mm³*		
1 (UP)	6	2	23.0	700	374	1.4	8	Marked hypoplasia (22, 33), moderate hypoplasia (75), mild hypoplasia (90)	Cyclosporine, corticosteroid, cefotaxime, cimetidine, captopril
2 (UP)	22	3	20.9	600	90	ND	9	Aplasia (31)	Cyclosporine, corticosteroid, cefotaxime, furosemide, ampicillin, aspirin, dipyridamole, hydralazine
3 (UP)	5	1	22.9	400	160	0.8	6	Marked hypoplasia (12, 19, 26)	Cyclosporine, corticosteroid, cefotaxime, ampicillin, clonidine, furosemide
4 (UP)	10	7	28.8	1100	720	0.8	15	Marked hypoplasia (55)	Cyclosporine, corticosteroid, cefotaxime, ranitidine, furosemide, ampicillin, captopril, hydralazine, nifedipine, metaclopramide
5 (UP)	7	3	24.3	300	120	2.6	8	Marked hypoplasia (43)	Cyclosporine, corticosteroid, cefotaxime, furosemide, phenobarbital, ampicillin, hydralazine, captopril
6 (UC)	10	7	14.0	400	0	0	10	Normocellularity (5), marked hypoplasia (45), aplasia (59)	Cyclosporine, corticosteroid, cefamandole, hydralazine, propranolol, captopril, trimethoprim–sulfamethoxazole, gentamicin, carbenicillin, methyldopa, ranitidine
7 (UC)	10	6	17.0	1100	66	0.2	7	Marked hypoplasia (55)	Cyclosporine, corticosteroid, cefoxitin, aspirin, hydralazine, ranitidine, furosemide
8 (UT)	3	1	21.0	500	21	0	25	Normocellularity (preoperative), marked hypoplasia (11), moderate hypoplasia (25)	Cyclosporine, corticosteroid, amikacin, trimethoprim–sulfamethoxazole, nafcillin, vancomycin, metronidazole, amphotericin B, furosemide, spironolactone, hydralazine, captopril
9 (UM)	12	3	18.0	700	63	0	12	Marked hypoplasia (39)	Cyclosporine, corticosteroid, azathioprine, chloramphenicol, amikacin, acyclovir, trimethoprim–sulfamethoxazole, captopril, propranolol, spironolactone, phenobarbital

*Representative low values before transfusion.

†Absolute neutrophil count (<800 = low). Representative low values before transfusion are shown.

‡ND denotes not determined. Representative low values before transfusion are shown.

[§]"Aplasia" indicates that blood-forming elements were absent; "marked hypoplasia," that they were very scarce; "moderate hypoplasia", that they were very scarce; and "mild hypoplasia," that they were reduced. Values in parentheses denote days after transplantation.

Table 3

Treatment of Aplastic Anemia and Outcome.

PATIENT NO.	ANTILYMPHOCYTE THERAPY*	OUTCOME
1 (UP)	Polyclonal ALG, 40 mg/kg/day for 14 days	Survival with normal marrow function and 4th graft, after primary nonfunction of 1st graft and rejection of 2nd and 3rd grafts (follow-up, 2 yr)
2 (UP)	Monoclonal OKT3, 0.12 mg/kg/day	Survival with partial recovery of marrow function (follow-up, 1 yr)
3 (UP)	None	Death during receipt of 3rd graft, after development of hepatitis in 1st graft and primary nonfunction of 2nd graft
4 (UP)	None	Survival with some recovery of marrow function (follow-up, <6 mo)
5 (UP)	None	Survival with some recovery of marrow function (follow-up, <6 mo)
6 (UC)	Polyclonal ATG, 12 mg/kg/day for 10 days	Death due to disseminated candida, intestinal hemorrhage
7 (UC)	Polyclonal ATG, 10 mg/kg/day for 10 days	Survival with no recovery of marrow function (follow-up, <6 mo)
8 (UT)	None	Death due to systemic aspergillosis
9 (UM)	Polyclonal ATG, 15 mg/kg/day for 5 days	Death due to systemic aspergillosis

*ALG denotes polyclonal antilymphocyte globulin, OKT3 monoclonal anti-OKT3 (Orthoclone OKT-3, Ortho), and ATG polyclonal antithymocyte globulin (Atgam, Upjohn).

Table 4

Occurrence of Aplastic Anemia, According to Indication for Orthotopic Liver Transplantation.

APLASTIC ANEMIA	INDICATION FOR TRANSPLANTATION				TOTAL
	ACUTE HEPATITIS			OTHER THAN HEPATITIS	
	non-A, non-B	A or B	nonviral*		
	number of patients				
Yes	9	0	0	0	9
No	23	12	22	1429	1486
	32	12	22	1429	1495

*Hepatitis induced by drugs (18 patients) or due to Wilson's disease (4 patients)