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Spontaneous remission of aplastic anemia: a retrospective analysis

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Background and Objectives. Although acquired aplastic anemia (AA) is usually a chronic disorder, a small proportion of patients with aplastic anemia has been reported to recover spontaneously without specific therapy such as allogeneic bone marrow transplantation or immunosuppressive treatment. We attempted to determine the rate of spontaneous remission in patients with AA.

Design and Methods. We reviewed the medical records of adult patients (n=136) who were diagnosed as having aplastic anemia at the Asan Medical Center from 1990 to 2000. The hematologic criteria of spontaneous remission were defined according to the proposed remission criteria of the SAA Working Party of the EBMT.

Results. Eighteen (13%) of 136 patients satisfied the criteria for spontaneous remission at a median of 14 days (range, 4-332) from the diagnosis of aplastic anemia. In fifteen (83%) of 18 patients, spontaneous remission occurred within 50 days. Spontaneous remission was complete in fourteen patients (78%). Only two patients relapsed at 208 and 1,857 days after spontaneous remission. Multivariate logistic regression analysis showed that the presence of infection at diagnosis (p = 0.017), a drug as an etiology of aplastic anemia (p = 0.028), and serum albumin level less than 3.4 g/dL (p = 0.005) were independent predictive factors for spontaneous remission.

Interpretation and Conclusions. Our study confirmed that a minority of patients with AA recovered spontaneously. Spontaneous remission was rapid and complete in most patients, and relapses were rarely observed. In most cases with spontaneous remission, aplastic anemia might associated with external factors such as a drug or infection.

Key words: spontaneous remission, aplastic anemia.

Aplastic anemia is a pathophysiologically heterogeneous, albeit phenotypically similar disease. This diagnosis includes a number of entities, which differ in behavior and prognosis. The fundamental defects may be congenital or acquired. Acquired aplastic anemia is usually a chronic disorder, whether it is idiopathic, or related to external factors such as hepatitis virus or exposure to a variety of non-cytotoxic drugs.[1-3] Virus- or drug-induced disorders selectively or preferentially involving a single cell lineage such as agranulocytosis, thrombocytopenia, or pure red cell aplasia are usually self-limited, and improve spontaneously after the causative agent is eliminated.[4,5] A small proportion of patients with aplastic anemia has also been reported to recover spontaneously.[1,2]

In this retrospective analysis, we attempted to determine the rate of spontaneous remissions in patients with aplastic anemia. The factors that can predict spontaneous remission of aplastic anemia were determined by multivariate analysis.

Design and Methods

Patients

All adult patients who were diagnosed as having acquired aplastic anemia at the Asan Medical Center, Seoul, Korea from January 1990 to March 2000 were included in the study. We retrospectively reviewed the medical records and collected the clinical, hematologic and other laboratory data.

Diagnosis of aplastic anemia

The diagnosis of acquired aplastic anemia was established according to published criteria.[6] At least two of the following three criteria had to be present: (a) hemoglobin $\leq$ 10 g/dL or hematocrit $\leq$ 30%, (b) platelets $\leq 50 \times 10^3/\mu L$, and (c) leukocytes $\leq$ 3,500/μL or neutrophils $\leq$ 1,500/μL. To confirm the diagnosis, there had to be an adequate bone marrow biopsy specimen showing the fol-

lowing: (a) a decrease in cellularity with the absence or depletion of all hematopoietic cells or normal cellularity due to focal erythroid hyperplasia with depletion of granulopoietic cells and megakaryocytes, and (b) the absence of significant fibrosis or neoplastic infiltration. Cases with pancytopenia due to cytostatic drugs or irradiation were excluded.

Patients were considered to have severe aplastic anemia if they had at least two of the following three peripheral blood values: (a) neutrophils < 500/μL, (b) platelets < 20×10^3/μL, and (c) reticulocytes < 1% (corrected for hematocrit). In addition, the marrow had to be either markedly hypoplastic (< 25% of normal cellularity) or moderately hypoplastic (25-50% of normal cellularity with < 30% of remaining cells being hematopoietic) as estimated from biopsies.[7] It was considered that the patient had very severe aplastic anemia if he or she met the criteria for severe disease and the neutrophil count was below 200/μL.[8]

Definition of spontaneous remission

Spontaneous remission was defined as hematologic recovery without specific therapy such as allogeneic bone marrow transplantation or any kind of immunosuppressive treatment including anti-thymocyte (or lymphocyte) globulin, cyclosporine, cyclophosphamide or corticosteroids. Hematologic recovery was defined according to the proposed remission criteria of the SAA Working Party of the EBMT: (a) the absence of the need for transfusions and (b) criteria of SAA not met in case of SAA, or improvement of at least one cell line (hemoglobin +3 g/dL if initially < 6 g/dL, neutrophils + 500/μL if previously < 500/μL, neutrophils $\times2$ or normal if previously ≥ 500/μL, platelets + 20×10^3/μL if previously <20×10^3/μL, or platelets $\times2$ or normal if previously ≥ 20×10^3/μL) in case of non-severe aplastic anemia.[9] Spontaneous complete remission was defined as all cell lines becoming normal for age and gender without specific therapy for aplastic anemia.

Statistical analysis

Individual characteristics were analyzed using the chi-squared test for prediction of spontaneous remission. Clinical and laboratory variables with a *p* value less than or equal to 0.1 by univariate analysis were considered for entry into subsequent multivariate analysis using the multiple logistic regression model. Among patients who achieved spontaneous remission, times to remission were calculated using the Kaplan-Meier method and compared by log-rank test.

Table 1. Clinical features of the patients with spontaneous remissions of aplastic anemia.

						Hematologic data at diagnosis						Time to	Time to	
Name	*Sex*	*Age*	*Severity*	*Etiology*	*Presenting symptom*	*Hb (g/dL)*	*cReti (%)*	*WBC (/μL)*	*ANC (/μL)*	*Platelets (×10³/μL)*	*BM cellularity*	*SpR (days)*	*SpCR (days)*	*Comment (days from diagnosis)*
JHL	M	24	NSAA	Phenytoin	Bleeding	7.1	–	3,300	693	41	25	132	350	Alive (3,038+)
HJL	M	40	SAA	Idiopathic	Anemia	8.0	0.71	2,600	754	19	10	7	283	Alive (844+)
CJK	F	59	NSAA	Herb medicine	Bleeding	9.8	1.89	2,100	1,302	38	10	33	221	Alive (473+)
HSY	F	65	VSAA	Idiopathic	Infection	5.8	0.04	800	200	7	5	18	198	Alive (1,375+)
JOH	F	42	VSAA	Methimazole	Infection	10.4	–	800	104	46	20	9	113	Alive (3,310+)
WJL	F	32	VSAA	Idiopathic	Infection	7.8	0.19	600	72	98	5	4	91	Alive (2,021+)
JSL	M	29	VSAA	Idiopathic	Infection	8.5	0.10	1,100	11	4	15	13	54	Alive (74+)
KHK	M	51	VSAA	Klebsiella	Infection	7.7	0.08	800	32	19	10	4	54	Died (123), Hepatic failure
KLK	F	47	VSAA	Herb medicine	Infection	9.1	0.07	600	12	5	15	21	49	Alive (293+)
JNI	F	52	VSAA	Idiopathic	Infection	9.0	0.13	800	64	2	10	14	38	Alive (777+)
SKM	M	64	VSAA	Idiopathic	Infection	9.4	0.06	200	2	4	10	19	34	Alive (1,285+)
YIK	M	47	VSAA	Mushroom	Infection	10.8	0.08	1,100	11	7	10	7	29	Alive (398+)
DSK	M	59	VSAA	Idiopathic	Anemia	6.3	–	600	6	4	10	8	27	Alive (2,618+)
HCI	M	59	VSAA	Pseudomonas	Infection	8.9	0.06	1,000	30	96	15	5	20	Alive (3,582+)
SKC	F	49	SAA	Idiopathic	Anemia	7.3	0.25	1,500	930	14	10	332	–	Alive (1,351+), Relapsed
BHY	F	26	SAA	Pregnancy	Bleeding	4.4	0.62	3,100	1,426	6	10	62	–	Died (2,908), Relapsed
OHP	F	70	SAA	Ticlopidine	Infection	9.1	0.04	500	25	12	10	32	–	Alive (1,103+)
JLL	F	49	VSAA	Ticlopidine	Infection	6.8	0.10	1,300	26	56	20	22	–	Alive (1,226+)

Hb = hemogloblin; cReti = corrected reticulocyte count; ANC = absolute neutrophil count; BM = bone marrow; SpR = spontaneous remission; SpCR = spontaneous complete remission; NSAA = non-severe aplastic anemia; SAA = severe aplastic anemia; VSAA = very severe aplastic anemia.

Results

Occurrence of spontaneous remission of aplastic anemia

Overall, 136 adult patients were confirmed to have acquired aplastic anemia at the Asan Medical center and were included in the study. Of these 136 patients, eighteen (13%) satisfied the criteria for spontaneous remission (Table 1). The median age of the 18 patients with spontaneous remission was 49 years (range 24-70). There were 8 males and 10 females. Two patients had non-severe aplastic anemia at diagnosis, four had severe aplastic anemia, and 12 had very severe aplastic anemia. The median cellularity of bone marrow biopsy was 10% (range, 5-25). In eight patients, aplastic anemia was idiopathic. Suspected etiologies of aplastic anemia in the other 10 patients were drugs in 7 patients, Gram-negative bacterial sepsis in two, and pregnancy in one. Presenting symptoms were infection in twelve patients, bleeding in three, and anemia in three. In twelve patients who presented with symptoms of infection, appropriate diagnostic tests such as blood cultures, chest X-ray, or others were performed. The median interval between the beginning of infection and the detection of cytopenia was 6 days (range, 1-14). The causes of the symptoms of infection were Gram-negative bacterial sepsis in two patients, pneumonia in two, tonsillitis in four, appendicitis in one, and neutropenic fever of unknown origin in three. One patient (SKM) received oxymetholone (50 mg/day) for 60 days, and five (KHK, KLK, JNI, OHP, and JLL) received granulocyte colony-stimulating factor (G-CSF) for 8-20 days. The median time to spontaneous remission from diagnosis was 14 days (range, 4-332 days). Five patients (28%) satisfied the criteria for spontaneous remission within 7 days. In fifteen (83%) of 18 patients, spontaneous remission occurred within 50 days (Figure 1). There was no difference in time to spontaneous remission between patients with idiopathic aplastic anemia (median 13 days) and drug-induced aplastic anemia (median 21 days) ($p = 0.587$). Time to spontaneous remission was significantly shorter in patients who presented with infection (median 13 days) than those who did not (median 33 days) ($p = 0.015$). Fourteen (77.8%) of 18 patients with spontaneous remission also reached spontaneous complete remission at a median of 54 days (range, 20-350) from the diagnosis of aplastic anemia. At a median follow-up of 1,256 days (range, 74-3,582 days), two patients, SKC and BHY, relapsed at 208 and 1,857 days after spontaneous remission,

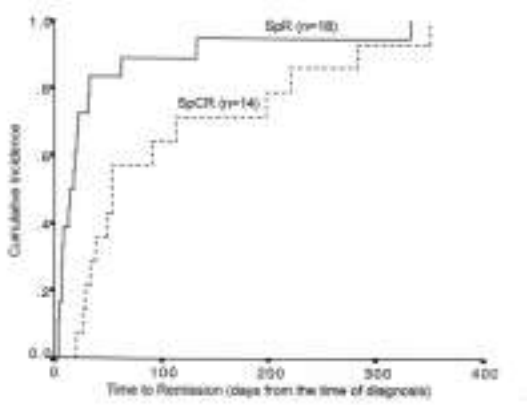

Figure 1. Time to SpR (spontaneous remission) in 18 patients and SpCR (spontaneous complete remission) in 14 patients from the diagnosis of aplastic anemia.

respectively. SKC, a 49-year old female, re-entered spontaneous remission 53 days after relapse and remained in partial remission until her last follow-up. BHY was diagnosed as having aplastic anemia during pregnancy and recovered spontaneously with the delivery of the baby. She relapsed 5 years later with aplastic anemia. Immunosuppressive treatment with antithymocyte globulin and cyclosporine was given without response. This patient died of aplastic anemia about 8 years after the initial diagnosis.

Factors predictive of spontaneous remission of aplastic anemia

To identify predictive factors for spontaneous remission of aplastic anemia, we analyzed various clinical and laboratory variables at the time of diagnosis of aplastic anemia. The patients' characteristics according to the occurrence of spontaneous remission are presented in Table 2. Sex distribution was similar between patients with or without spontaneous remission. The proportion of patients younger than 40 years was smaller in patients with spontaneous remission ($p = 0.003$). Infection was a most common presenting symptom in patients with spontaneous remission, but it was an infrequent presentation in patients without spontaneous remission ($p < 0.001$). Most patients (89%) with spontaneous remission had severe or very severe disease at the time of diagnosis of aplastic anemia, whereas 64% of patients without spontaneous remission had severe or very severe aplastic anemia ($p = 0.001$). The pattern of transfusion dependency was not significantly different according to the

Table 2. Patient characteristics at the time of diagnosis according to the occurrence of spontaneous remission of aplastic anemia.

Characteristic	*Patients with SpR*	*Patients without SpR*	*p-value*
Total number of patients	18	118	
Sex, M/F	8/10	48/70	0.762
Age (years)			0.003
< 40	4	70	
≥ 40	14	48	
Presenting symptoms			< 0.001
None	0	13	
Anemia	3	61	
Infection	12	12	
Bleeding	3	31	
Other	0	1	
Severity at diagnosis			0.001
Non-severe	2	42	
Severe	4	47	
Very severe	12	29	
Transfusion dependency			
Transfusion independent	6	20	
RBC dependent	0	11	
Platelet dependent	2	9	
RBC & platelet dependent	10	78	
Etiology of aplastic anemia			< 0.001
Idiopathic	8	104	
Drug	7	6	
Hepatitis virus	0	5	
Immune disease	0	3	
Pregnancy	1	0	
Bacterial infection	2	0	

SpR = spontaneous remission.

occurrence of spontaneous remission. Drugs were frequently associated with aplastic anemia in patients with spontaneous remission, but most patients without spontaneous remission had idiopathic aplastic anemia ($p < 0.001$).

In univariate analysis of laboratory variables at the time of diagnosis of aplastic anemia, hemoglobin ≥ 7.0 g/dL ($p = 0.011$), neutrophils < 500/μL ($p = 0.018$), lymphocytes < 1,000/μL ($p = 0.001$), monocytes < 50/μL ($p = 0.018$) and serum albumin level < 3.4 g/dL ($p < 0.001$) favored the occurrence of spontaneous remission (Table 3).

With multivariate analysis using a multiple logistic regression analysis, presence of infection at diagnosis ($p = 0.020$; RR = 12.14), a drug as an etiology of aplastic anemia ($p = 0.018$; RR = 8.98), and serum albumin level less than 3.4 g/dL ($p = 0.007$; RR=12.19) were independent predictive factors for the occurrence of spontaneous remission of aplastic anemia (Table 4).

Table 3. Hematologic and other laboratory data at the time of diagnosis according to the occurrence of spontaneous remission of aplastic anemia.

Characteristic	*Patients with SpR*	*Patients without SpR*	*p-value*
Hemoglobin (g/dL)			0.011
< 7.0	4	64	
≥ 7.0	14	54	
Corrected reticulocyte count (%)			0.224
< 1.0	14	61	
≥ 1.0	1	15	
Platelets (/μL)			0.752
$< 20 \times 10^3$	12	83	
$\geq 20 \times 10^3$	6	35	
Neutrophils (/μL)			0.018
< 500	13	50	
≥ 500	5	68	
Lymphocytes (/μL)			0.001
< 1,000	13	39	
≥ 1,000	5	79	
Monocytes (/μL)			0.018
< 50	13	50	
≥ 50	5	68	
Bone marrow cellularity (%)			0.318
< 10	2	25	
≥ 10	16	93	
Albumin (g/dL)			< 0.001
< 3.4	11	12	
≥ 3.4	7	105	
Aspartate aminotransferase (IU/L)			0.402
< 41	14	100	
≥ 41	4	17	
Alanine aminotransferase (IU/L)			1.000
< 41	14	91	
≥ 41	4	26	
Bilirubin (mg/dL)			0.828
< 1.3	15	95	
≥ 1.3	3	22	
Hepatitis B virus surface antigen			0.138
Negative	11	95	
Positive	3	9	
Antinuclear antibody			0.238
Negative	11	63	
Positive	2	4	

SpR = spontaneous remission.

Discussion

Spontaneous reconstitution of hematologic parameters in patients with aplastic anemia has been reported in case reports and in studies which investigated the natural course of aplastic anemia. There have been case reports about spontaneous remission of aplastic anemia under different designations, such as transitory bone marrow failure, transient aplastic anemia, reversible bone marrow aplasia, or transient bone marrow aplasia.[10] In an old report

Table 4. Multivariate analysis of predictive factors for the occurrence of spontaneous remission of aplastic anemia.

Variables	*Risk ratio*	*95% confidence interval*	*p value*
Age (years)			
≥ 40 vs. < 40	3.72	0.63-22.02	0.148
Presenting symptoms			
Infection vs. others	12.14	1.47-99.94	0.020
Severity at diagnosis			
Severe vs. Non-severe	6.39	0.59-69.19	0.127
Etiology of aplastic anemia			
Drug vs. others	8.98	1.46-55.23	0.018
Hemoglobin (g/dL)			
≥ 7.0 vs. < 7.0	4.17	0.82-21.24	0.086
Neutrophils (/μL)			
< 500 vs. ≥ 500	14.82	0.97-226.67	0.053
Lymphocytes (/μL)			
< 1,000 vs. ≥ 1,000	0.90	0.16-4.94	0.901
Monocytes (/μL)			
< 50 vs. ≥ 50	5.86	0.85-40.22	0.072
Albumin (g/dL)			
< 3.4 vs. ≥ 3.4	12.19	1.98-74.99	0.007

that investigated 60 patients with acquired aplastic anemia, nine patients (15%) were in a state of remission.[2] In an analysis of 174 patients with aplastic anemia, eighteen (10%) had spontaneous remission.[1] A report from the *International Agranulocytosis and Aplastic Study* described transient pancytopenias both with hypoplastic and with non-hypoplastic marrow.[11] Twelve (5%) of 224 patients with a hypoplastic bone marrow (classified as aplastic anemia) showed a fast recovery, usually within 4 weeks. In our study, 13% of patients with aplastic anemia showed spontaneous remission at a median of 14 days after diagnosis, and this interval is also the time required for complete evaluation of cytogenetics, morphology and progenitor cell cultures. At this time point one should know whether a patient qualifies for a spontaneous remission. Considering that early introduction of effective therapy such as allogeneic bone marrow transplantation or immunosuppressive treatment is emphasized in severe aplastic anemia,[12] the incidence of spontaneous remission in our study may be underestimated. Most patients with spontaneous remission in our study showed spontaneous improvement of blood counts during the treatment of infection or the preparation for allogeneic bone marrow transplantation. Although early treatment is important to avoid infection and sensitization from multiple transfusions in aplastic anemia, it is still advisable to delay treatment if a clear upward trend of blood counts is observed.[10]

Recovery of hematopoietic cell production was rapid and complete in most of our patients with spontaneous remission. Five patients satisfied the criteria for spontaneous remission within one week, and the median time to spontaneous remission was only two weeks from the diagnosis of aplastic anemia. Spontaneous remission was complete in 14 of 18 patients, and only two relapses were observed at a median follow-up of 1,256 days (range, 74-3,582 days). These findings are in a striking contrast to those in patients who received immunosuppressive treatment such as anti-thymocyte (or lymphocyte) globulin or cyclosporine. Responses after immunosuppressive treatment are usually delayed and incomplete, and relapses are frequent.[13] In our patients with spontaneous remission, external factors might have been associated with the aplastic anemia, and the hematologic findings might have rapidly and completely recovered with the eradication or withdrawal of external factors.

With multivariate analysis, presence of infection at diagnosis, drugs as an etiology of aplastic anemia, and serum albumin level less than 3.4 g/dL were independent predictive factors for spontaneous remission. While infection was an infrequent presentation in all patients with aplastic anemia, it was the most common presenting symptom in patients with spontaneous remission. Time to spontaneous remission was significantly shorter in patients who presented with infection than those who did not. Many patients spontaneously recovered from pancytopenia during antibiotic treatment of infection. These findings suggested that infection might trigger the process of aplastic anemia. A history of drug exposure was found in 7 patients with spontaneous remission, and a drug was a possible etiology of aplastic anemia in these cases. Hypoalbuminemia at the diagnosis of aplastic anemia was also an independent predictive factor for spontaneous remission. Hypoalbuminemia in acutely ill patients is due to increased catabolism rather than to a decreased rate of albumin synthesis, and it is one of the acute phase reactions.[14,15] In our hypoalbuminemic patients without liver function impairment, the low albumin level might have been related to an acute insult by external factors. The findings that infection, a history of drug exposure, and hypoalbuminemia were independent predictive factors for spontaneous remission suggested that external factors

might have been responsible for the occurrence of aplastic anemia in most of our patients with spontaneous remission. In the same manner, associations with external factors have been well defined in agranulocytosis, thrombocytopenia, or pure red cell aplasia.[4,5,16,17]

In conclusion, our study confirmed that a minority of patients with AA recovered spontaneously. Spontaneous remission was rapid and complete in most patients, and relapses were rarely observed. In most cases with spontaneous remission, aplastic anemia might have been associated with external factors such as a drug or infection.[4,5,16,17]

Contributions and Acknowledgments

JHL[1] (Je-Hwan Lee), JHL[2] (Jung-Hee Lee), and KHL contributed equally to this work and were primarily responsible for it, from conception to submitted manuscript: they should be considered as the principal authors. JHL[2] and YRS collected the clinical data. HSC and CJP examined bone marrow slides of the patients. JHL[1] and JHL[2] prepared the manuscript. JSL and WKK were involved in critically revising the content of the manuscript. KHL gave the final approval for its submission. Order of authorship. Authors are listed according to a criterion of decreasing individual contribution to the work, with the following exceptions: the first two authors contributed equally to this article, while the last author had a major role as senior author in designing the study, interpreting the data and preparing the article.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Potential implications for clinical practice

We confirm that a minority of patients with aplastic anemia recover spontaneously without specific treatment. Although early treatment is important to avoid infection and sensitization from multiple transfusions in aplastic anemia, it is still advisable to delay treatment if a clear upward trend of blood counts is observed.

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