ORIGINAL ARTICLE

Aplastic Anemia in Children

by

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Abstract

During a period of 5 years (1975-1980) nine children with aplastic anemia were admitted to the Department of Child Health, Gadjah Mada University Hospital, Yogyakarta. They were 6 boys and 3 girls from 4 to 12 years of age. Of all the patients, 7 could be classified as the acquired type, and 2 as the idiopathic type. Generally, they were admitted with the following chief complaints : paleness, weakness and bleeding manifestations (skin bleeding 100%, bleeding of mucous membrane 44,4%). All of them showed pancytopenia. Eight patients showed normocytic normochromic anemia and one patient had microcytic hypochromic anemia. Seven patients had aplastic bone marrows, the other two hypoplastic. All patients received prednison and oxymetholon.

Only one got remission after getting therapy for eight months. Six of nine patients died (66,6%). Four of the six death were caused by bleeding (44,7%), and two others might be caused by sepsis and bleeding (33,3%).

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Introduction

Aplastic anemia is characterized by severe anemia, leucopenia, thrombocytopenia with aplastic or hypoplastic of bone marrow and usually with a normal size spleen (Kempe et al., 1976).

Generally the complaints are paleness, weakness, and often followed by fever and bleeding manifestations. This disease was reported firstly by Ehrlich in 1888 (Wintrobe, 1974), while the term "Aplastic Anemia" was used for the first time by Chauffard in 1904 (Miale, 1972).

There are 3 general types of aplastic anemia in childhood: idiopathic aplastic anemia, secondary/acquired aplastic anemia, and Fanconi's congenital pancytopenia (Kempe et al., 1976; Rahman et al., 1976). Congenital aplastic anemia which is not accompanied by other congenital anomalies was found firstly by Estren and Dameshek (Miale, 1972).

The etiologic factor is obscure, but the acquired type of aplastic anemia may be the influence of radiation, cytostatica which produce bone marrow depression. Some chemical and other drugs such as benzen, phenothiazin, sulfonamides, phenylbutazon etc. especially chloramphenicol are considered potentially myelotoxic (Bloom and Diamond, 1968). Furthermore viral hepatitis is considered as the cause of acquired aplastic anemia.

Some therapeutical efforts have been done including corticosteroid and androgen treatment (singly or in combination), splenectomy, bone marrow transplantation and supportive therapy such as blood transfusion and preventive measures against infection (Wintrobe, 1974).

Aplastic anemia is a serious disease, the treatment of which needs special facilities, but the result is still not satisfactory and even mostly are fatal ending.

Usually the patients are sent to the hospital in a seriously ill condition and they have received various drugs before such as: roborantia, hematinics, anticoagulantia etc., which in fact are useless.

The purpose of this study is to present some aspects of aplastic anemia cases, particularly concerning the clinical and laboratory picture and the results of treatment in the Department of Child Health, Gadjah Mada University Hospital Yogyakarta.

Materials and methods

The cases reported below consisted of 9 patients admitted to the Department of Child Health, Gadjah Mada University Hospital in a five-year period (1975-1980).

The diagnosis was based on anamnesis, physical examination, laboratory investigation of peripheral blood picture and bone marrow aspirate. Blood chemistry examination was done according to indication.

Sex, age, date on admission, the history of illness included chemical exposures, radiation exposure, drugs and viral hepatitis which may produce this disease,

were recorded. The criteria for suspected involvement of agents (chemical/drugs) were history of exposure during six months before the onset of symptoms and four months for viral hepatitis (Lewis, 1965; Rahman et al., 1976).

Peripheral blood examination was repeated every week, and bone marrow aspirate was done every month.

The diagnosis of aplastic anemia was established by the presence of pancytopenia with aplasia/hypoplasia of bone marrow besides anamnesis and clinical course of the disease, such as anemia with all its manifestations, bleeding with all the effects, with or without infection.

All the patients were treated with prednison 1 mg/kg body weight/day and oxymetholon 5 mg/day. Other treatment included blood transfusion and administration of antibiotic on indication.

Remission was evaluated from the improvement of the clinical status such as decrease of hemorrhages, requiring no additional blood transfusion etc., and peripheral blood and bone marrow picture.

Results

In the period of January 1975 until December 1980, 9 patients were diagnosed as aplastic anemia, consisted of 6 boys and 3 girls. Most of them were native Indonesian, one was Chinese.

Before admission they had received various drugs such as roborantia (100%), hemostatics and hematinics (77,8%). Nine of the patients had a history of radiation exposure, only one patient had suffered from viral hepatitis i.e. 3 months before the symptoms of aplastic appeared, 6 patients had taken chloramphenicol and acetyl salicylic acid (bodrexin tablet) within 6 months before the onset, while two patients were doubtfull (table 1). On admission all patients showed

TABLE 1: *Drugs/chemical agents which are suspected to be the cause (anamnesis)*

Case no.	Sex	Age	Drugs/chemical agents/others
1	M	11 years	chloramphenicol bodrexin (salicylate)
2	M	10 years	?
3	F	5 years	kemicetin/chloramphenicol bodrexin (salicylate)
4	M	9 years	chloramphenicol
5	F	11 years	viral hepatitis
6	M	8 years	chloramphenicol bodrexin (salicylate)
7	M	4 years	?
8	F	12 years	chloramphenicol bodrexin (salicylate)
9	M	6 years	bodrexin (salicylate)

weakness, pallor, fever and bleeding manifestations such as: petechia and ecchymosis (100%), epistaxis (44%) and gum bleeding in 4 patients (44,4%) (table 2).

TABLE 2 : *Hemorrhagic diathesis in 9 patients with aplastic anemia*

Case no.	Type of hemorrhage
1	epistaxis, ecchymosis
2	epistaxis, ecchymosis
3	ecchymosis, gum bleeding
4	epistaxis, ecchymosis
5	ecchymosis, gum bleeding
6	ecchymosis, gum bleeding
7	ecchymosis, epistaxis; petechiae
8	ecchymosis, petechiae
9	ecchymosis, gum bleeding

On physical examination all of them were severely anemic without splenomegaly, hepatomegaly and lymphadenopathy. All the patients admitted were in a seriously ill condition.

Blood hemoglobin level 2-8 gm%, leucocyte counts 1500-6300/mm^3, thrombocyte counts 3000-56000/mm^3, reticulocyte count 6‰ in 2 patients and the rest were under 3‰ to zero (table 3a).

TABLE 3a : *Hematologic data on admission*

Case no.	Ht (%)	Hb (%)	Erythrocyte count/mm^3	Type of anemia	Reticulocyte count	
					%	/mm^3
1	8	3	1.050.000	normocytic normochromic	0	0
2	15	5,4	2.590.000	"	3	7.770
3	6	2	1.750.000	microcytic hypochromic	0	0
4	18	6	1.950.000	normocytic normochromic	7	13.671
5	17	6	2.210.000	"	0	0
6	10	3	2.460.000	"	1	2.400
7	8	2,7	1.030.000	"	1	1.030
8	8	2,8	1.080.000	"	6	6.480
9	25	8,2	2.070.000	"	0	0

All patients had positive tourniquet test, prolonged bleeding time and poor clot retraction. Bone marrow examination showed aplasia in 6 children, hypoplasia in 2 patients. One patient at first showed hypoplasia of erythropoietic and thrombopoietic system, but after a week she showed aplastic bone marrow (table 3b).

TABLE 3b : *Hematologic data on admission*

Case no.	Leuco. /mm^3	Granulo		Lympho (%)	Thrombo. /mm^3	Bone marrow
		%	mm^3			
1	2.800	26	728	74	12.000	aplasia
2	4.000	12	480	88	14.000	aplasia
3	1.500	13	195	87	20.000	hypoplasia
4	6.300	17	1.071	82	52.000	aplasia
5	3.100	9	279	91	4.000	aplasia
6	3.750	20	750	80	25.000	aplasia
7	3.600	18	648	72	10.000	aplasia
8	3.900	34	1.326	66	56.000	hypoplasia
9	3.100	10	310	89	30.000	aplasia

There were no side effect of the treatment. Only one patient got remission after eight months therapy and the others never achieved remission until death. Out of these nine patients 1 was lost for follow up, 7 died. The causes of death were thought to be mainly due to hemorrhages alone in four patients, and hemorrhages with sepsis in three patients. One patient who is still alive did not achieve remision (table 4).

Discussion

During five years there were 9 cases of aplastic anemia at the Department of Child Health, Gadjah Mada University Hospital (0,15% of total admissions). Compared with other Child Health Departments within a five-year period, there were 22 cases in Jakarta; 12 cases in Surabaya from 8452 patients admitted (0,14%), and 22 cases in Bandung from 6271 patients admitted (0,35%) (Markum et al., 1969; Untario et al. 1970; Rahman et al., 1976).

We found a higher incidence in males similar to that found by Markum et al., 1969 and Untario et al., 1970. Other author did not find any difference in sex distributions (Scott et al., 1959; Lewis, 1965; Rahman et al., 1976). Seven patients could be classified as the acquired type and two patients as the idiopathic type.

The cause of bone marrow failure could not be elicited in 2 cases. Chloram-

TABLE 4 : *Treatment and out-come in 9 cases of aplastic anemia*

Case no.	Treatment			Complications		Remission	Follow up	Out come
	pred.	oxy-meth.	trans-fus.	inf.	bleeding			
1	+	+	+	—	+	—	3 months	died
2	+	+	+	—	+	—	6½ "	died
3	+	+	+	+	+	—	1½ "	died
4	+	+	+	—	+	after 8 months	9 "	*
5	+	+	+	+	+	—	10 "	died
6	+	+	+	—	+	—	5 "	died
7	+	+	+	—	+	—	18 days	lost for follow-up
8	+	+	+	+	+	—	3½ months	**
9	+	+	+	—		—	1 weeks	died

Note :
* lost for follow up
** still alive until December 1980 in a good condition, first diagnosed 15th August, 1980.

phenicol as the cause were suspected in one case, whereas salicylate and a combination of chloramphenicol with salicylate in 1 case and 4 cases respectively.

Davis and Rubin (1972) found that 24% of their cases were caused by chloramphenicol, while Bloom and Diamond (1968); Frederick et al., 1972; Rahman et al., 1976 found 36,6%, 27,5% and 13,6% respectively.

Although its mechanism was not clear yet most writers believed that there was a relationship between chloramphenicol and bone marrow aplasia.

Chloramphenicol could cause vacuolization and depression of the erythropoietic and hemopoietic system (Awwad, et al., 1975; Bachtin et al., 1978), reticulocytopenia and vacuolization of blast cell in the bone marrow (Curdy, 1963).

poietic and hemopoietic system (Kamel, 1975; Bachtin et al., 1978), reticulocytopenia and vacuolization of blast cell in the bone marrow (Curdy, 1963).

In vitro the effects of chloramphenicol on chromosome are: breakdown, fragmentation and intra-chromosome vacuolization (Mitus and Coleman, 1970). Bone marrow suppression by chloramphenicol occurred as the result of protein synthesis inhibition of mitochondria and finally suppression of heme synthetase (ferrochelatase), so there was a blockade to the last step of heme-synthesis (Junis, 1975).

No much study has been done yet on the influence of salicylate upon bone marrow, but there was an assumption that it had a myelotoxic effect (Bloom and Diamond, 1968). Cases reported by Rahman et al. (1976) revealed that 18,1% of the cases may be caused by salicylate and our study suggested a figure of about 11%.

One of our cases may be caused by viral hepatitis. Alyouni and Doeblin (1974) collected data on aplastic anemia which was caused by viral hepatitis from previous authors. They found 90 cases included 2 of their cases.

The relationship between viral hepatitis and aplastic anemia was obscure but thrombocytopenia and granulocytopenia were known for a long time as the hematologic abnormalities in the first stadium of viral hepatitis (Conrad et al., 1964).

It was known that the mitosis of leucocyte in patient with viral hepatitis was suppressed and its serum could inhibit mitosis of normal leucocyte.

There was a latent period between the onset of viral hepatitis and the appearance of aplastic anemia. Alyouni and Doeblin (1974) found that 80% cases had a latent period of about 10 weeks. Twelve weeks were the interval between hepatitis and the appearance of aplastic anemia in one patient of our study.

The clinical manifestations in our patients did not differ from those mentioned in the literature. Hemorrhagic diathesis was found in all patients. The types of hemorrhages in the patients on admission can be seen in table 2. On admission most of the cases showed a normocytic normochromic blood picture (8patients); one patient showed microcytic hypochromic anemia, this patient also suffered from ankylostomiasis.

The mortality was high (66,6%) similar to the reports of other authors. In Boston 71% of 58 cases of acquired aplastic anemia died (Frederick et al., 1972) and in Bandung the mortality reported was 57% of 14 cases who could be followed up (Rahman et al., 1976).

The treatment with anabolic-androgenic-steroid gave 53,4% response; with corticosteroid only 11,7% response (Petry et al., 1968; Suparman et al., 1978), while with androgen the remission was 40-50% (Junis, 1975). In our 9 cases the treatment with anabolic-androgenic steroid resulted in remission only in one case.

Most literature stated that the prognosis of aplastic anemia depended on many factors such as: the severity of bone marrow failure (Shahidi et al., 1961; Deposito et al., 1964), the severity of thrombocytopenia and granulocytopenia (Lewis, 1965), fetal hemoglobin level (Bloom et al., 1968; Abdul Sallam et al., 1972).

Four hematologic criteria i.e. reticulocyte count, thrombocyte count, neutrophil count and bone marrow aplasia could be used as parameters to predict the prognosis (Himawan et al., 1976).

Our six patients who died showed neutrophil count less than 1000/mm^3 and platelet count less than 20.000/mm^3; in agreement with Lewis criteria for a poor

prognosis. Markum et al. (1969) stated that the value of neutrophil count 2000/mm^3 and platelet count less than 20.000/mm^3 were capable to predict a poor prognosis because it needs a longer treatment with testosteron and corticosteroid compared with the patient who have higher neutrophil and platelet count. Our four patients who died showed reticulocyte counts less than 20.000/mm^3, neutrophil counts less than 500/mm^3, thrombocyte counts less than 30.000/mm^3 and bone marrow aplasia. This condition indicated a poor prognosis (Himawan et al., 1976).

Bloom and Diamond (1968) and Abdul Salam et al. (1972) reported that the Hb F level of less than 400 mg% showed a bad prognosis. Hb F examination was done on only four patients. All of them showed a level of Hb F less than 400 mg%. Out of these four patients, one was lost for follow up and three died.

Summary

Nine cases of aplastic anemia has been reported. Seven patients could be classified as the acquired type and two patients as the idiopathic type.

The cause of the disease could not be elicited in 2 cases. Chloramphenicol as the cause was suspected in 2 cases, whereas salicylate and a combination of chloramphenicol and salicylate in one case and four cases respectively.

Treatment consisted of blood transfusion and a combination of prednison-oxymetholon. Only one case achieved remission after 8 months therapy.

Seven out of nine patients died, one patient was lost for follow up. The authors conclude that the prognosis of aplastic anemia in children especially with aplasia of bone marrow is very poor.

REFERENCES

1. ABDUL SALAM, M.; MARKUM, A.H.; MUSLICHAN, S.; ODANG, O.: Prognostic value of fetal hemoglobin level in aplastic anemia. Paediatr. Indones. 12 : 360 (1972).
2. ALYOUNI, K.; DOEBLIN, T.D.: The syndrome of hepatitis and aplastic anemia. Br. J. Haemat. 27 : 345 (1974).
3. AWWAD, S.; KHALIFA, A.S.; KAMEL, K.: Vacuolization of Leucocyte and Bone Marrow Aplasia due to Chloramphenicol Toxicity. Clin. Pediat. 14 : 499 (1975).
4. BACHTIN, M.; SUTARYO; SUNARTO; HARUN AL RASYID dan ISMANGOEN: Pengaruh Pengobatan Chloramphenicol terhadap sumsum tulang. Buku Abstrak KONIKA IV 21-25 Mei, Yogyakarta hal. 111 (1978).
5. BLOOM, G.E.; DIAMOND, L.K.: Prognostic value of fetal hemoglobin level in acquired aplastic anemia. New Engl. J. Med. 273 : 304 (1968).
6. CONRAD, M.E.; SCHWARTZ, F.D.; YOUNG, A.A.: Infectious hepatitis - a generalized disease. A study of renal, gastrointestinal and hematologic abnormalities. Am. J. Med. 37 : 789 (1964).
7. CURDY, P.R.: Plasma concentration of chloramphenicol and Bone Marrow Suppression. Blood 21 : 363 (1963).
8. DAVIS, S.; RUBIN, A.D.: The treatment and prognostic in aplastic anemia. Lancet ii : 871 (1972).

9. DEPOSITO, F.; AKATSUKA, J.; THACHER, L.G.; SMITH; N.J.: Bone marrow failure in pediatrics patients. Cortison and testosteron treatment. J. Pediat. 64 : 863 (1964).
10. FREDERICK, P.L.; BLANCHE, P.A.; DAVID, G.N.: The mortality of acquired aplastic anemia in children. Blood 40 : 153 (1972).
11. HIMAWAN, T.; SETIAWAN, M.; TJAHJONO, T.; KHO, L.K.: Prognostic value of some hematologic parameters in aplastic anemia. Kongrs. Nas. II Perhimpunan Hematologi & Transfusi Darah Indonesia, Surabaya 8-9 Oktober, 1976.
12. JUNIS, A.A.: Mekanisme Patogenetik Kerusakan Sumsum Tulang akibat Pengaruh Obat. Medika, No. 1 : 8-9 (1975).
13. KEMPE, C.H.; SILVER, H.K.; O'BRIEN: Aplastic anemia in Current Pediatric Diagnosis and Treatment; 4th ed., p. 365 (Maruzen Asian Ed., Tokyo 1976).
14. LEWIS, S.M.: Course and prognosis in aplastic anemia. Br. Med. J. 1 : 1027 (1965).
15. MARKUM, A.H.; ISKANDAR, W.; KHO, L.K.; ODANG, O.: Studies on panmyelopathies in Djakarta. Paediatr. Indones. 9 : 143 (1969).
16. MIALE, J.B.: Aplastic anemia; in Laboratory Medicine Hematology; 4th ed., p. 939 (Mosby, Saint Louis 1972).
17. MITUS, W.J.; COLEMAN, N.: In vitro effect of Chloramphenicol on chromosomes. Blood 35 : 680 (1970).
18. PETRY, J.G.; BUNCH-STROOMANN, H.A.; HIENZ, T.H.; SINCE; JMA-USS: Androgen treatment without inhibiting effection hypophysis and male gonads. Acta endocr. 59 : 3 (1968).
19. RAHMAN, O.; ASIKIN, J.; WIRIADI-SURIA, S.: Aplastic anemia. Paediatr. Indones. 16 : 146 (1976).
20. SHAHIDI, N.T.; DIAMOND, L.K.: Testosteron-induced remission in aplastic anemia of both acquired and congenital types : Further observation in 24 cases. New Engl. J. med. 264 : 953 (1961).
21. SCOTT, J.L.; CARTWRIGHT, G.E.; WINTROBE, M.M.: Acquired aplastic anemia analysis of 39 cases and review of pertinent literatures. Medicine 38 : 119 (1959).
22. SOEPARMAN, A.; HARYANTO, R.; TAMBUNAN, K.L.; ZUBAIRI, D.: Pengalaman pengobatan penderita anemia aplastik yang didapat (acquired) di Fakultas Kedokteran Universitas Indonesia R. S.C.M. Naskah Lengkap KOPAPDI IV Bandung hal. 1379, 1978.
23. UNTARIO, S.; TANTRI, J.; SUNARWAN: Aplastic anemia. Paediatr. Indones. 10 : 7 (1970).
24. WINTROBE, M.M.: Clinical Hematology; 7th ed., pp. 1744-1769 (Lea Febiger, Philadelphia 1974).