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Clinico-Haematological and Management Profile of Aplastic Anaemia – A First Series of 18 Cases from Nepal

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ABSTRACT

Aim of Study: To study the prevalence, clinico-haematological and management profile of aplastic anaemia (AA) among severely anaemic patients treated at BP Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal.

Method: A retrospective analysis of 18 cases of biopsy proven AA patients was done between September 1995 and August 1997.

Results: Over a period of 2 years, 140 patients with severe anaemia were admitted to our institution. Eighteen patients were diagnosed with AA. The ages of the AA patients ranged from 7 to 56 (median 15) years, with a male : female ratio of 1.23:1. Pallor, bleeding diathesis, weakness and fever were the most common presenting complaints. Blood counts showed pancytopenia in 16 cases. Bone biopsies of all the cases were hypoplastic. Sixteen cases were non-severe AA and the remaining 2 were severe. Of the 18 cases, 16 were idiopathic; 1 case each was associated with chloramphenicol toxicity and hepatitis B infection respectively. Most of the patients were treated with corticosteroids or androgens or a combination of both. Only six patients came for regular follow-up.

Conclusion: The high (12.85%) prevalence of AA among patients admitted with severe anaemia in this hospital (which acts as a catchment area for the Eastern region) may not reflect the actual prevalence of the disease in the local community. However, a prospective study may delineate the causative factors peculiar to this region.

The clinico-haematological profile is typical of the disease. However, the management profile is incomplete without a proper follow-up. This limitation may be overcome by providing free or subsidised treatment.

Keywords: anaemia, aplastic, prevalence, haematology, management, Nepal

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INTRODUCTION

Aplastic anaemia (AA) is a rare disease and its true incidence is uncertain. However, there is an unexplained geographic variation leading to an increase in its incidence in the orient as compared to that in the West[1-6].

Most cases of aplastic anaemia are acquired. The bone marrow failure may be secondary to physical, chemical and infectious insults or nutritional deficiencies. However in many cases, the etiology is unknown. Advances in cell biology, virology, toxicology, and immunology have brought better realisation of the complex interactions involved in the pathobiology of this disorder. The diagnosis of aplastic anaemia depends entirely on the laboratory evaluations ie., bone marrow biopsy and peripheral blood examinations. The introduction of bone marrow transplantation for the treatment of aplastic anaemia in 1969 by Thomas et al[7] led to the search for well defined criteria not only for the diagnosis of acquired aplastic anaemia but also for judging its severity.

AA usually presents at BP Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal as cases of severe anaemia not responding to treatment or requiring repeated blood transfusion. A search of the literature on AA in Nepal yielded a single report of two cases[8]. To fill this lacuna, it was decided to determine the prevalence of AA among severely anaemic patients treated at BPKIHS and also to highlight their clinico-pathological and management profiles.

MATERIAL AND METHODS

All case histories from the hospital records of severe anaemic inpatients admitted from September 1995 to August 1997 were scrutinised for the purpose of this study. Cases of AA which were confirmed by bone marrow biopsy only were further analysed for their clinico-haematological profile on their first visit to our centre. Eighteen cases of aplastic anaemia, from a total of 140 patients of severe anaemia, worked up at BPKIHS, were retrieved from the files of the Department of Pathology and Medical Record Section. Detailed clinical history, laboratory investigations, treatment regimes and follow-up of each patient were noted from these files.

The hypoplastic marrow was classified as moderately and markedly hypocellular[11]. The cases were further categorised as severe aplastic anaemia (SAA) and non-severe aplastic anaemia (NSAA) on the basis of peripheral blood counts and bone marrow appearance as per the criteria laid down by the

International Aplastic Anaemia Study Group Criteria for Severe Aplastic Anaemia[11], in an attempt to highlight its prognostic value:

Peripheral blood	Neutrophils $< 0.5 \times 10^9$/L
	Platelets $< 20 \times 10^9$/L
	Reticulocytes < 1% (corrected for haematocrit)
Bone marrow trephine	Markedly hypocellular, < 25% cellularity
	Moderately hypocellular, 25% – 50% normal cellularity with < 30% of remaining cells haematopoietic

Severe aplastic anaemia is defined by any two or three peripheral blood criteria and either marrow criteria.

RESULTS

Over a period of two years, 140 patients with severe anaemia were admitted either to the Medical or Paediatrics ward of the hospital for investigation to find out the cause of anaemia. Eighteen patients (12.85%) were diagnosed as AA. All the cases were from the Eastern region of Nepal, where the hospital is located, and one-third (N = 6) of these cases belonged to the Tharu community. A detailed past history revealed no cause in the majority of the cases. One patient (Case 10) was treated with chloramphenicol for typhoid fever 3 months prior to the clinical manifestation of AA. The other patient (Case 4) gave a history of jaundice 2 months prior to admission and was found to be HbsAg positive. Physical examination revealed no hepatosplenomegaly or lymphadenopathy in any case.

Clinical manifestations (Table I)

The ages of the patients ranged from 7 to 56 (median 15) years with a peak between 10 and 30 years. The male and female ratio was 1.25:1. The common presenting symptoms in order of decreasing frequency were pallor, bleeding diathesis in the form of bleeding from gum and/or nose, bruising or petechial rashes, followed by generalised weakness and fever. The interval between onset of symptoms and first visit to the hospital ranged from 15 days to 3 years (mean 6.27 months).

Laboratory findings (Table I)

The peripheral blood count showed pancytopenia in majority of the cases (N = 16). Blood smear showed red blood cells (RBCs) of normochronic and normocytic morphology in most of the cases (N = 16). Only two cases showed RBCs of macrocytic morphology with moderate anisopoikilocytosis. The corrected reticulocyte count ranged from 0.2% to 0.9% (mean 0.5%). The differential white cell count showed neutropenia and relative lymphocytosis in most of the cases (N = 15). Immature myeloid leukocytes were not seen in any of the cases. The bleeding time was normal or mildly prolonged (2 cases) and prothrombin time was normal in all cases.

The bone marrow smears showed numerous spicules with empty fat spaces and only few haemopoietic cells. Lymphocytes and plasma cells were prominent. The bone marrow biopsy showed moderate (N = 11) to marked (N = 5) hypoplasia in 16 cases. In 2 cases (Cases 10 and 18), the marrow was hypoplastic with focal cellular areas where the touch imprints revealed moderately cellular marrow consisting of all 3 series of haematopoietic cells. Sixteen cases were categorised as non-severe aplastic anaemia and only 2 cases (Cases 4 and 16) as severe aplastic anaemia.

Treatment and follow-up (Table II)

There was a history of blood transfusion (whole blood) in all cases either before admission or during their stay in hospital. The total number of blood transfusions (whole blood) ranged from 1 to 21 (mean 5.72) units of blood over a period of 1 to 18 (mean 4.11) months of the disease. All patients were prescribed a combination of corticosteroids (oral prednisolone 1mg/kg/day in divided doses) and androgens (oral oxymethalone 2mg/kg/day) and were told to come for follow-up on a monthly basis. Eight patients did not report for follow-up. Of the remaining 10 patients, one pregnant patient (Case 11) died of septicaemia following intrauterine fetal death during her stay in hospital; 6 patients (1 SAA and 5 NSAA) came for regular check-ups and 3 patients were lost to follow-up. The duration of follow-up ranged from 1.5 to 14 months (mean 6.33 months). All the patients who came for follow-up resided in the district where the hospital is situated. These patients who received treatment were symptomatically better and their blood counts rose to satisfactory levels. One patient of NSAA (Case 6) required regular blood transfusion in spite of treatment with corticosteroid and androgen. Subsequently, the patient was put on cyclosporin (oral solution 8mg/kg/day) and improved symptomatically.

DISCUSSION

Aplastic anaemia (AA) is a rare disease characterised by a failure of blood cell production resulting in varying degrees of pancytopenia with marked hypocellular bone marrow. Most cases of AA are acquired and its true incidence is not known for defined populations in most countries. More recent surveys in Western Europe[1,2] and the United States[3] suggest that the incidence is in the order of 3 – 5 in 1 million population/year. The incidence in the Far East, particularly China and Southeast Asia, is higher than that in the West[1-6]. Except for a single report of 2 cases[8], no other literature is available from Nepal on AA.

The prevalence of AA appears to be high (12.85%) among severe anaemia cases admitted in the wards of this hospital, which serves as a tertiary referral centre for the Eastern region of Nepal. Six cases (33.33%) were from the Tharu community, an ethnic population residing in this region. No racial predisposition for AA has been reported in the literature. Reports of the incidence rates of AA among defined populations is scarce[2,3]. It is necessary to explore why one-third of the cases in the study belonged to the Tharu community. As farming is the main occupation of this community, the effect of cumulative exposure to pesticides, a commonly used chemical, may probably be an important etiologic

Table I – Haematological profile of patients with aplastic anaemia

Case no.	Hb (g/L)	PCV (L/L)	TLC ($\times 10^9$/L)	PC ($\times 10^9$/L)	CRC (%)	ANC ($\times 10^9$/L)	Bone marrow smears (aspirate/imprint)	Bone biopsy
1	60	0.22	3.0	50	0.9	1.95	Markedly hypocellular	Moderate hypoplasia
2	30	0.15	2.5	20	0.8	0.80	NA	Moderate hypoplasia
3	44	0.16	3.1	20	0.3	1.24	NA	Moderate hypoplasia
4	25	0.15	2.1	22	0.6	0.39	NA	Marked hypoplasia
5	50	0.21	3.1	55	0.5	1.33	Moderately hypocellular	Moderate hypoplasia
6	30	0.18	1.9	43	0.4	0.53	Moderately hypocellular	Moderate hypoplasia
7	30	0.19	2.8	57	0.5	0.78	Markedly hypocellular	Marked hypoplasia
8	36	0.20	3.5	33	0.8	1.47	NA	Moderate hypoplasia
9	32	0.19	2.2	40	0.3	0.88	Markedly hypocellular	Marked hypoplasia
10	57	0.21	2.6	36	0.5	1.56	Moderately cellular	Hypoplastic marrow with focal cellular area
11	26	0.19	2.9	33	0.2	0.84	Markedly hypocellular	Moderate hypoplasia
12	49	0.21	5.2	55	0.5	2.65	Moderately hypocellular	Moderate hypoplasia
13	30	0.18	4.1	33	0.3	2.66	Moderately hypocellular	Moderate hypoplasia
14	44	0.20	2.1	35	0.4	0.67	Markedly hypocellular	Marked hypoplasia
15	45	0.20	3.0	40	0.7	1.02	NA	Moderate hypoplasia
16	22	0.14	1.9	45	0.5	0.095	Markedly hypocellular	Marked hypoplasia
17	56	0.20	4.0	47	0.6	1.96	Moderately hypocellular	Moderate hypoplasia
18	31	0.15	1.4	22	0.2	0.58	Moderately cellular	Hypoplastic marrow with focal cellular area

Hb : Haemoglobin, PVC : Packed cell volume, TLC : Total leucocyte count, PC : Platelet count, ANC : Absolute neutrophil count, CRC : Corrected reticulocyte count, NA : Not available

Table II – Clinical and management profile of patients with aplastic anaemia

Case no.	Age (yr)	Sex	Duration of symptoms at first visit	Total no. of blood transfusions in units* received during treatment (period in months)	Drug treatment (Duration in months)	Follow-up (Duration in months)
1	30	M	3 years	2 (1)	Nil	NFU
2	11	M	1 month	2 (1)	Nil	NFU
3	56	M	6 months	21 (9)	CS + A (8)	7 months
4	12	F	18 days	7 (7)	CS + A (2)	1.5 months
5	7	F	15 days	10 (18)	CS + A (15)	14 months
6	34	M	1.5 years	19 (10)	CS + A (9) + C (2)	10 months
7	29	F	3 months	4 (4)	CS + A (3)	2.5 months
8	21	F	6 months	4 (4)	CS + A (2)	LFU
9	15	F	1 year	7 (6)	CS + A (4)	3 months
10	30	M	1 month	2 (1)	Nil	NFU
11	16	F	7 months	6 (1)	Nil	Died
12	11	M	8 months	3 (2)	CS + A (2)	LFU
13	10	M	2 months	2 (1)	Nil	NFU
14	34	M	2 months	4 (4)	CS + A (2)	LFU
15	14	F	2 months	2 (1)	Nil	NFU
16	8	M	1 month	4 (2)	Nil	NFU
17	26	M	1 year	1 (1)	Nil	NFU
18	14	F	15 days	3 (1)	Nil	NFU

M : Male, F : Female, + : Present, CS : Corticosteroid, A : Androgen, C : Cyclosporin, LFU: Lost follow-up, NFU : No folllow-up

* Includes all blood transfusions received before and during stay at this hospital.

agent[9], among other causes. The ages of the patients ranged from 7 to 56 years with a peak between 10 and 30 years and a slight preponderance of males as reported in the literature[3]. A cluster of AA cases has been described in teenagers[9].

Clinical manifestations and blood findings of the cases were similar to the reports in the literature. The failure of haematopoiesis in AA may not be total, and patches of active haematopoiesis may remain[10] so that aspirate may yield relatively normal looking marrow as found in two of our cases. The assessment of cellularity for the diagnosis of AA should be made on trephine biopsy and not be limited to a bone marrow aspirate/imprint alone. This also helps to exclude other causes of pancytopenia and to determine the severity of the disease at any particular time. Majority of cases were categorised as non-severe aplastic anaemia (NSAA) and only two cases (Cases 4 and 16) as severe aplastic anaemia (SAA).

The treatment of AA has two main components. Firstly, to protect and support the patient from the consequences of pancytopenia and secondly, to try to accelerate the recovery of the bone marrow by whatever means. Before marrow transplantation and immunosuppressive therapy was available, more than 25% of the patients died within 4 months of diagnosis and 50% within 1 year[11,12]. In a multicenter study of patients with severe aplastic anaemia, no difference in survival was noted between patients treated with bone marrow transplantation and those treated with immunosuppression[13]. The best response to androgens is observed in patients with less aggressive and milder disease[14]. The combination of androgens with corticosteroids appears to improve the results as compared to androgens alone. Use of high dose of corticosteroids has been reported to be effective as single-agent immunosuppressive agent[15].

All our patients had received blood transfusion either before admission or during their stay in the hospital. Of the six patients who came for regular follow-up, five showed good clinical improvement and blood counts on a combination of corticosteroids and androgens therapy. One case continued to require increased number of blood transfusions but he responded with the addition of cyclosporin. In our setup, where no bone marrow transplantation facility is available, and with most of our patients belonging to the low socioeconomic group, treatment with androgen and corticosteroid appears to be encouraging. Immunosuppressive agents can be added to those who can afford it.

A multivariate analysis reported that the interval between onset and first visit, bone marrow non-myeloid cellularity, sex, bleeding symptoms and the severity of reticulocytopenia, neutropenia, and thrombocytopenia were all predictive for AA[16]. These prognostic factors could not be further assessed in our study as the number of patients were too small.

No cause could be identified in the majority of cases. One case was associated with chloramphenicol toxicity and another with hepatitis B virus infection. Most cases of acquired aplastic anaemia are idiopathic. Drug toxicity, hepatitis and radiation injury are major causes of secondary AA[2,17,18].

The high prevalence of aplastic anaemia in this study may be attributed to the fact that this is a major referral hospital for the Eastern region of Nepal. Thus this may not reflect the actual prevalence in the local population. We advocate that all pancytopenia cases should be exhaustively investigated before a diagnosis of aplastic anaemia is made. Also, incentives in the form of free or subsidised treatment may increase follow-up rates. A more detailed prospective study may delineate etiologic factors peculiar to this country or region, if any.

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