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Original Research Article.

Clinico-Hematological Profile of Aplastic Anemia in Southern Odisha: An Institutional Study

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ABSTRACT

Introduction: Aplastic anemia is a potentially life-threatening failure of hematopoiesis, characterized by pancytopenia and hypocellular bone marrow. Aplastic anemia if untreated results in very high mortality. Early diagnosis of Aplastic anemias is essential for appropriate management of the patient.

Aims and Objectives: The aim of the study was to assess the prevalence of the condition in southern odisha admitted to this institute and to study the clinico-hematological profile for the assessment of severity by using the modified Camitta criteria aiding in their management protocol.

Materials and Methods: This study was carried out prospectively in the Department of Pathology, MKCG Medical College & Hospital during the period of June 2017 to May 2019. A detailed clinical history, physical examination, Complete Blood Count, CPS, Reticulocyte count, Bone marrow aspiration and Biopsy were performed in each case and the observations were evaluated using simple and basic statistical tools.

Results: There are 63 diagnosed cases of aplastic anemia during the study period. Out of 63 cases 36 cases are male (57.14 %) and 27 cases are female (42.86 %) indicating a male preponderance of this disease and male to female ratio is 1.3: 1. We also found that, Aplastic anemia has a bi modal age distribution. Fever, generalized weakness and bleeding due to thrombocytopenia are commonest clinical manifestations. All 63 cases are sub categorized into 38 Non severe cases (60.32 %), 17 severe cases (26.98 %) and 8 cases are very severe (12.70 %).

Conclusion: A good knowledge on clinical and hematological parameters will certainly aid in early diagnosis of Aplastic anemia and sub-categorization for treatment. But in a developing country financial constraints and lack of awareness forms a major drawback in patient management. So early diagnosis of Aplastic Anemia reduce the treatment cost as well as will decrease mortality.

Keywords: Hematological Profile, Aplastic Anemia, Hematopoiesis.

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INTRODUCTION

Aplastic anemia is a potentially life-threatening failure of hematopoesis, characterized by pancytopenia and hypocellular bone marrow. The pathophysiologic characteristic of this disorder is injury to or loss of pluripotent hematopoietic stem cells in the absence of infiltrative disease of the bone marrow.[1]

Aplastic anemia affects people of all ages and all races. There is a little male predominance of this disease.[2] The age distribution is bimodal, with peaks in (15-25 yrs) and elderly (>60 yrs).[3,4]

The frequency of aplastic anemia seen in hospitals of Asian countries is 2-3 times higher than reported from the West. At present, the overall incidence of the disease in general population is three to six per million, considering both inherited as well as acquired aplastic anemia.[5] The incidence of aplastic anemia has been progressively increasing over the last few decades, This may be due to exposure to environmental factors, genetic background, diagnostic criteria, use of drugs and chemicals and study designs. More than 70% patients with acquired aplastic anemia are idiopathic i.e. no cause can be determined.[4,6] In the rest of the cases, the major identifiable etiological factors are exposure to ionizing radiations, chemicals like benzene, some viruses like Parvovirus B19 and a number of drugs like chloramphinicol, gold, sulphonamides and cytotoxic drugs. Pregnancy is also a risk factor for aplastic anemia, but in most of the pregnant ladies it recovers by itself when pregnancy is over.[3,7]

There is a paucity of data on aplastic anemia from India because of limited number of studies. Our study was conducted to describe the Clinico –heamatological profile of 63 aplastic anemia cases diagnosed at our centre during the study period.

MATERIALS AND METHODS

This prospective study was carried out in the Department of Pathology, MKCG Medical College &Hospital during the period of June 2017 to May 2019. Approval from the Institutional Ethical Committee was obtained prior to the beginning of the study. A total of 63 cases of aplastic anemia are diagnosed in this study satisfying the inclusion criteria.

The inclusion criteria were based on the criteria laid down by the International Agranulocytosis and Aplastic anemia Study group, 1987[8], which is defined as:

(1) Peripheral blood showing at least two out of three of the followings:

a. Hemoglobin less than 10 g/dl or hematocrit less than 30%.
b. Total leukocyte count less than 3.5 × 10^9/l or granulocyte count less than 1.5 × 10^9/l.
c. Platelet count less than 50 × 10^9/l.

(2) Bone marrow biopsy showing the following:

a. Decrease in cellularity with absence or depletion of all hematopoietic cells < 25%.
b. Absence of significant fibrosis or neoplastic infiltration.

Patients who do not give consent for the procedure, patients having pancytopenia and a cellular marrow on bone marrow aspiration or biopsy and patients having pancytopenia and hypocellular marrow, but with neoplastic infiltration were excluded from the study. Informed consent was obtained from patients and from guardians in the case of minors.

The following laboratory investigations were carried out in all patients:

1. A detailed clinical history, physical examination and available previous investigations were recorded.
2. Complete blood count, including reticulocyte count.
3. Peripheral blood film examination.
4. Bone marrow aspiration and biopsy.

Collection of bone marrow samples were carried out in the procedure rooms at the department under proper aseptic conditions and after administration of a local anesthetic over right posterior superior iliac spines. Pediatric patients were presedated with intravenous ketamine. About 0.5 ml of bone marrow aspirate sample was drawn out in each case and smeared. Trephine biopsy samples were obtained from areas little distance from aspiration site. Attempts were made to yield a biopsy length of at least 2.5 cm. The core biopsy samples had undergone fixation in 10% formalin for 24 h and decalcification in 20% EDTA for 12 h. Thereafter, paraffin blocks were made and slides were prepared. All peripheral blood films and bone marrow aspiration were air-dried and stained with Leishman stain. The biopsy slides were stained with hematoxylin and eosin.

Lastly assessment of severity of all patients was done by using the modified Camitta criteria.

I. Severe AA: Marrow cellularity <25% (or 25-50% with < 30% residual hematopoietic cells), plus at least 2 of:
   a) Neutrophils< 0.5 x 10^9/l;
   b) Platelets < 20 x 10^9/l;
   c) Reticulocyte count <20 x 10^9/l.
II. Very Severe AA; As for Severe AA but neutrophils < 0.2 x 10^9/L
III. Non severe AA; AA not fulfilling the criteria for severe or very severe AA.

RESULTS

There are 63 diagnosed cases of aplastic anemia during the study period satisfying the inclusion criteria. Out of 63 cases 36 cases are male (57.14 %) and 27 cases are female (42.86 %) indicating a male preponderance of this disease and male to female ratio is 1.33: 1.[Table 1]

We also found that, Aplastic anemia has a bimodal age distribution. One peak at adolescent age and another peak at elderly.[Table 2]

Fever 42 cases, generalized weakness 34 cases and bleeding manifestations 14 cases are commonest clinical manifestations followed by easy fatigability 12 cases and breathlessness 04 cases. Purpura, bleeding per vagina and per rectal bleeding and gum bleeding was the most common bleeding manifestations.[Table 3]

Patients presenting with fever had total leukocyte count ranged from 440/µl to 3200/µl, with mean value around 1200/µl, whereas absolute neutrophil count in those patients ranged between 112/µl and 1480/µl, with mean values close to 660/µl.[Table 4]

Purpura is minute bleeding manifestation whereas bleeding per vagina and per rectal bleeding and gum bleeding were the gross bleeding manifestations. Patients having minute bleeding had platelet count between 11,000/µl and 41,000/µl, with mean values being around 23,000/µl . Patients presenting with gross bleeding had platelet count ranging from 4,000/µl to 35,000/µl, with mean value around 16,000/µl.[Table 5]

All 63 cases are sub categorized into 38 Non severe cases (60.32 %), 17 severe cases (26.98 %) and 8 cases are very severe (12.70 %).[Table 6]

During the procedures for collection of bone marrow samples, no serious complication such as bleeding, needle break, and local anesthetic reaction were noted. Local hematoma formation in six (9.52 %) patients. In nine (14.28 %) patients, bone marrow aspiration procedures were met with blood tap. Patients were followed up for up to 2 weeks after the procedures, and no complication was encountered.

Table 1: Shows Gender Distribution

Gender	n	%
Male	36	57.14%
Female	27	42.86%
Total	63	100%

Table 2: Shows Age Distribution of the Patients

Age groups (years)	n	%
0–15	10	15.87 %
16–30	18	28.57 %
31–45	09	14.28 %
46–60	11	17.46 %
>60	15	23.82 %

Table 3: Shows Clinical Manifestations.

Clinical features	n	%
Fever	42	66 %
Generalized weakness	34	54 %
Bleeding manifestations	14	22.22 %
Easy fatigability	12	19.04 %
Breathlessness	04	6.35 %

Table 4: Correlation between Fever and Leukocyte Count and Absolute Neutrophil Count

Clinical presentation	Leukocyte count(/µl)		Absolute Neutrophil count(/µl)	
Fever	**Range**	**Mean**	**Range**	**Mean**
	440-3200	1820	112-1480	660

Table 5: Correlation between Bleeding Manifestations and Platelet Count.

Bleeding manifestations	n	Platelet range/µl	mean
Minute bleeding manifestation	3	11,000/µl and 41,000/µl	23,000/µl
Gross bleeding manifestations	11	4,000/µl to 35,000/µl,	16,000/µl.

Table 6: Shows Severity of Disease

Severity	Male	Female	Total cases [*n* (%)]
Very severe	5	3	8 (12.70)
Severe	11	6	17 (26.98)
Nonsevere	22	16	38(60.32)

DISCUSSION

During the study period there were 63 diagnosed cases of aplastic anemia satisfying the inclusion criteria age ranged from 6years to 78 years. Out of 63 cases 36 cases are male (57.14 %) and 27 cases are female (42.86 %) indicating a male preponderance of this disease and male to female ratio is 1.33: 1.In the study by Kumar et al.[9] the age ranged from 12–63yrs. There was a male preponderance and the male to female ratio was 1.4:1.In the study by Jha et al [2] the age ranged from 1.5–70yrs (17yrs). There was male preponderance with male to female ratio of 1.3:1.Montane et al [4], showed that there is a biphasic distribution, with peaks at 10-25 years and over 60 years similar to our study.

The commonest clinical feature was that of fever 42(66%), followed by generalized weakness 34 (54%). Anemia leads to fatigue, whereas neutropenia to increased susceptibility to infections which cause fever. In the study of Tariq Aziz et al.[10] Pallor and generalized weakness (98%) are common clinical feature and in the study of Shano Naseem et al.[11] Fever (51.8%) is the common clinical feature.

The Hemoglobin concentration ranged from 2.9-5 gm/dl in Jha et al[2] and 1.3-8 gm/dl in kumar et al[9]. In our study Hemoglobin concentration ranged from 2-9.8 gm/dl. The TLC count ranged from 900–3800 /µl in Jha et al[2] and 200– 3000 /µl in kumar et al[9].

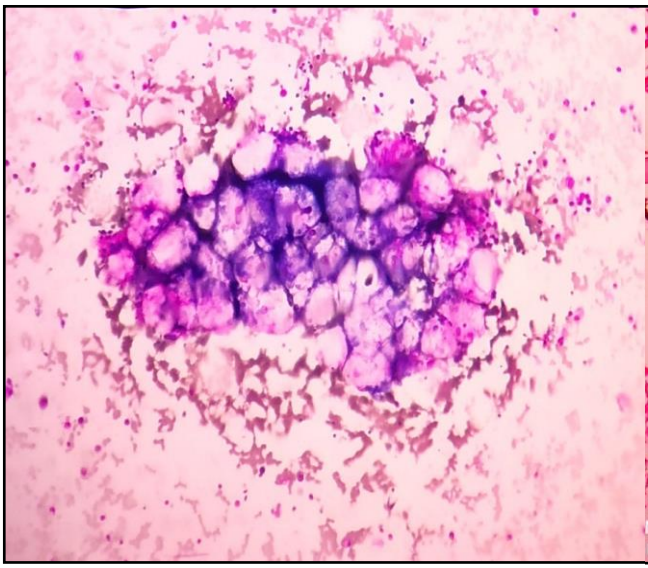

Figure 1: Bone marrow aspiration showing hypocellular marrow particles. Particle shows only fat cells.

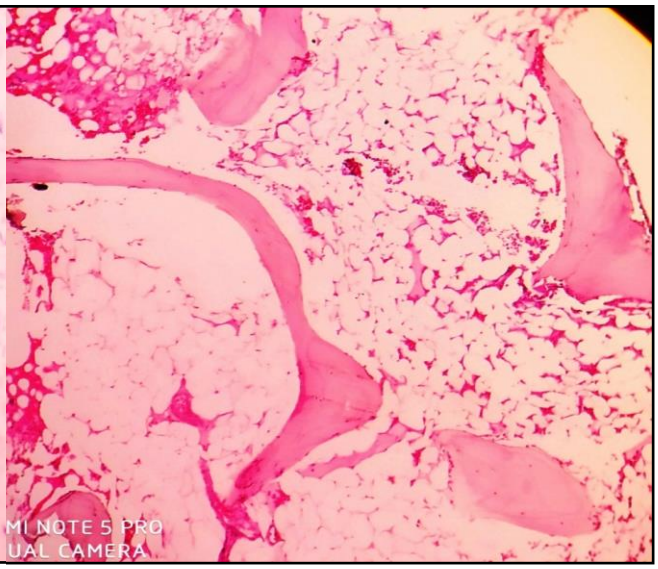

Figure 2: Bone marrow Biosy showing hypocellular marrow.

In our study TLC ranged from 530– 3200/µl. The platelet count ranged from 1000–1.36000 /µl in jha et al[2] and 8000–86,000/µl in kumar et al[9]. In our study platelet count ranged from 4000 – 5700/µl. In the study by Tilak Jain et al[12] 2 / 6 th patients had anisocytosis and 3 / 6th patients had relative lymphocytosis. In the study by Daniel N. M et al[13] he found normocytic normochromic erythrocytes in 64 %, macrocytic normochromic blood picture in 20 %.In the present study 68.2 % had normocytic normochromic erythrocytes. 86.3 % of them had relative lymphocytosis. Cellularity of bone marrow in aplastic anemia is very much reduced. It can be hypocellular or acellular. Lymphocytes and plasma cells are prominent.

Daniel N M et al[13] in their analysis of 50 cases reported 74 % of patients with hypocellular marrow, 16 % of patients had normocellular marrow which later became hypocellular.10 % had acellular marrow. In the present study, Bone marrow was hypocellular and the aspirate was mostly composed of fat cells in all the patients [Fig-1]. There was relative increase in plasma cells and lymphocytes. Bone marrow trephine biopsy revealed 92 % are hypocellular [Fig-2] and rest 8% are acellular and marrow is replaced by fat cells.

Severe and very severe Aplastic anemia were more common than non-severe aplastic anemia in many studies[2,9] . But our study showed more of non-severe aplastic anemia, probably because the comparison data were from the referral centers. The assessment of degree of disease severity is important in treatment decisions. Bone marrow Biopsy specimens are obtained in all the 63 diagnosed patients of aplastic anemia. Despite repeated attempts of bone marrow aspirations, 9 (14.28%) patients were met with bloody tap.No adverse event such as bleeding, needle

break, local anesthetic reaction, or death was encountered. Only local hematoma formation was observed in 6 cases (9.52%) patients. Patients were followed up for up to 2 weeks after the procedures, and no complication such as infection was documented. In a study conducted by Barbara J. Bain[14] on 54 890 biopsy samples, adverse events were seen in 26 (0.047%) cases, mostly comprising hemorrhage in 14 (0.028%), needle-related incidents in seven (0.014%), and infection in three (0.006%) cases. None of the patients having hemorrhage suffered from aplastic anemia. Six of those 14 cases with hemorrhage needed blood transfusion, and one patient ultimately died of bleeding. Our observations are in agreement with that of Barbara J. Bain in that there was no incidence of bleeding in aplastic anemia.

Regarding bone marrow aspiration, 9 are bloody tap, in 44 cases bone marrow particle are hypocellular and in rest 10 cases, there were a few normocellular particles admixed with predominantly hypocellular particles. The bone marrow biopsy findings were compatible with the diagnosis of aplastic anemia in all the patients. In cases where normocellular particles were seen in the background of predominantly hypocellular particles it was difficult to describe the overall cellularity of the bone marrow depending upon aspiration smears. This may be due to aspiration from an area of bone marrow in which hematopoiesis is not affected to its full extent. In such cases biopsy is informative.

Bone marrow biopsy was the tool that gave us the final and accurate details of marrow cellularity and proportions of each individual cellular element. It nullified the bias created by normocellular particles in marrow aspiration smears. All the problems of assessing marrow cellularity arising from blood tap and pauci cellular smears were solved by biopsies. All cases were eventually diagnosed by means of bone marrow biopsy findings, combining with findings of peripheral blood, bone marrow aspirations. Finally, we can conclude that bone marrow biopsy can be taken as the gold standard for diagnosing marrow suppression in aplastic anemia; however, cellular morphology interpretation is better in aspiration as compared with biopsies.

The combination of evidences obtained from clinical details, peripheral blood pancytopenias, hypocellular marrow particles in aspirate smears, can be accepted as fast and dependable findings for diagnosing aplastic anemia, without waiting for the biopsy report, which takes a longer period of processing. This may help the clinician to initiate a prompt treatment in critically ill patients.

CONCLUSION

Aplastic anemia, a potentially fatal disease, can occur in any age group, although mostly affects adolescents and elderly. It presents with clinical symptoms and signs, resulting from suppression of hematopoiesis — for example fever, generalized weakness, fatigue, pallor, and purpuric spots. Fever was more common with low absolute neutrophil count. The severity of bleeding manifestations correlated with the severity of thrombocytopenia. Although bone marrow aspiration helps in diagnosing marrow aplasia or hypoplasia, the confirmative diagnosis rests upon bone marrow biopsy examination, as it gives more precise information about marrow cellularity and also excludes several other causes of hypocellular marrow aspirate. Bone marrow biopsy is indeed necessary to differentiate aplastic anemia from hypocellular myelodysplastic syndrome and myelofibrosis. Although bone marrow biopsy is necessary for diagnosis, the haematological parameters are important for classifying severity and aid in treatment. But in a developing country like India financial constraints and lack of awareness forms a major drawback in patient management. So early diagnosis of Aplastic Anemia reduce the treatment cost as well as will decrease mortality.

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