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Original Article

Spectrum of Aplastic Anaemia: Presentation, Etiology and Overall Survival-A Tertiary Care Hospital Experience

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ABSTRACT

Aplastic Anemia (AA) is a hematological disorder with immune pathophysiology. There is a decrease in bone marrow precursors and cellularity which lead to a peripheral decline in at least two cell lines. The incidence of AA is higher in the Asian population as compared to that in the west. **Objective:** To highlight the disease spectrum of aplastic anemia patients from the clinical presentation and etiological factors to the disease outcome and overall survival. **Methods:** It was a descriptive cross-sectional study. The study was conducted at Hematology Department King Edward Medical University from March 2017 to March 2020.All the patients of both genders, diagnosed with AA on peripheral smear and bone marrow trephine biopsy findings were included and those with inherited AA, Myelodysplastic syndrome (MDS), acute leukemias and myelofibrosis were excluded from the study. After taking consent of university review board, all the data including personal information, detailed past history for risk factors, drug history, medical history, physical examination, investigations, performance score, treatment details and outcome of included patients were obtained using self-designed questionnaires for individual patient. The patients were followed up, the results were recorded and data was analyzed using SPSS V22. **Results:** The study included total 91 patients of AA out of which 46(50.5%) were males, 45(49.5%) were females. The peak incidence was seen in the age range 15-30 years. The patients were divided into three groups according to the severity of which moderate aplastic anemia was present in 19(20.9%) patients, severe AA was seen in 42(46.2%) patients and very severe AA was seen in 30(33%) patients. The etiological factors seen included idiopathic 61.5%, hakim medication 14.3%, infections 12% drugs 9.8% and radiation exposure 2.1%. It was observed that the patients with severe AA presented with high ECOG score. Total 59 patients died in one year causing mortality rate of 64.8%. Highest mortality rate was seen in very severe AA **Conclusions:** Aplastic anemia has life detrimental outcome with high mortality rate if left untreated can be provided to the patients since it is one of the high incidences hematological disorder in Asian population.

INTRODUCTION

Aplastic Anemia is approximately 1-1.5 % higher in Southeast Asia. It is ranked 2nd in prevalence in hematological disorders in Pakistan [1,2]. An immune mechanism is considered as the underlying mechanism for the development of AA in most idiopathic cases. Involvement of T-lymphocytes has been suggested due to the overexpression of HLA DR 2 in the diagnosed patients. This implies the role of immunosuppressants in the treatment of aplastic anemia. In other cases, factors attributing to the disease include drugs mainly sulphonamides, chloramphenicol, penicillin, carbamazepine, allopurinol, pesticide, and radiation exposure [3,4]. Hepatitis-associated AA follows acute illness by virus. The symptoms of the disease are attributed to the decrease in the cell lines. These include bleeding, pallor, generalized fatigue, dyspnea, fever, recurrent infections, epistaxis, bruises over the body, and so on [5,6]. On the basis of severity, AA is divided into three categories. Non-severe disease has neutrophil count < 1.5×109/L, platelet count <100×109/L and hemoglobin < 10 g/dL. The severe disease includes two of three blood counts of an absolute neutrophil count < 0.5×10 9 /L, platelet count <

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20×10 9 /L, and reticulocytes <1% whereas very severe disease has extreme neutropenia (<0.2×10 9 /L) [7]. AA affects Asians 2 to 3 times more than persons in other parts of the world [8]. For successful treatment of AA, early diagnosis and treatment, as well as long-term monitoring, are critical [9]. In a developing country like Pakistan, the prevalence of AA is much higher as compared to developed countries. Unfortunately, few definitive studies are conducted here to find the association of etiological factors. This study has highlighted the disease spectrum of AA patients from the clinical presentation to the disease outcome and overall survival. It aims at finding the various etiological factors which may influence or contribute to the development of AA.

METHODS

It was a descriptive cross-sectional study conducted at Hematology Department King Edward Medical University from March 2017 to March 2020. All the patients of both genders, diagnosed with AA on peripheral smear and bone marrow trephine biopsy findings were included in our study. To diagnose AA, Camitta and modified Camitta criteria for severe AA [7] were followed which include: 1. Absolute neutrophil count (ANC) < 500/UL, 2. Platelet count <20,000/UL 3. Retic count < 1% corrected or < 20,000 cell /UL. 4. Bone marrow cellularity < 25% according to age. The patients with suspected inherited aplastic anemia on the basis of clinical criteria and laboratory investigations were excluded from the study. Similarly, patients who had Myelodysplastic syndrome (MDS), acute leukemias and myelofibrosis were excluded from the study by observing parameters like dysplasia in all three cell lineages, blast percentage, pearls iron test and trichrome reticulin stain. After taking consent of University review board, all the data including personal information, detailed past history for risk factors, drug history, medical history, physical examination, investigations, performance score, treatment details and outcome of included patients were obtained using self-designed questionnaires for individual patient. The CBC and peripheral smear findings including hemoglobin levels, ANC, platelet and retic count and bone marrow biopsy findings were obtained. Bone marrow aspirate and trephine biopsy were examined by two expert hematologists on two different occasions to exclude observational bias. Findings including morphology, cellularity and architecture of bone marrow were observed. Immunohistochemistry was done to exclude the presence of any other disease. The standard treatment as per the institute's policy was started with cyclosporin and ATG, depending upon the availability. Supportive treatment was given to the patients as per requirement. The patients were followed up, the results were recorded and data was analyzed using SPSS V22. Descriptive analysis was done for categorical variables like age, gender using mean SD. Continuous variables were assessed using percentages. ECOG score was calculated and presented in the form of graph and Kaplan meirre survival curve was obtained to look for overall survival.

RESULTS

The study included total 91 patients of AA out of which 46(50.5%) were males, 45(49.5%) were females with male to female ratio 1.02:1. The mean age of all patients was calculated to be 30 years SD 17 years and median was 21 years. The mean age for male and female patients was 25 +/- 16 years and 22 +/- 11.2 years respectively. The peak incidence was seen in the age range 15-30 years. The patients were divided into three groups according to the severity of aplastic anemia in which moderate aplastic anemia was present in 19 (20.9%) patients, severe AA was seen in 42 (46.2%) patients and very severe aplastic anemia was seen in 30 (33%) patients. The distribution of severity of aplastic anemia and age groups is described in table 1. The clinical presentation, examination findings and laboratory investigations of all patients are summarized in Table 2.

Aplastic anemia	Age groups			Total N%
	1-15 years, N%	15-30 years, N%	>30 years, N%	
Moderate (MAA)	06 (20%)	13 (28.3%)	None	19(20.9%)
Severe (SAA)	16 (53.3%)	23 (50%)	03 (20%)	42 (46.2%)
Very severe (VSAA)	08 (26.7%)	10 (21.7%)	12 (80%)	30(33%)
Total	30 (33%)	46(50.5%)	15(16.5%)	

Table 1: Patients of Aplastic Anemia according to Age groups and Severity.

Variables	Present (n)	%
Presenting features		
Fever	60	65.9%
Bleeding (Bruises, petechia, epistaxis)	51	56%
Fatigue/lethargy	45	49.5%
Infection	41	45.1%
Clinical examination		
Pallor	59	64.8%
Bruises/petechia	33	36.3%
Shortness of breath	31	34.1%
Bleeding (nose, gums etc.)	12	13.2%
Etiological factors		
Antibiotics	05	5.5%
Antimalarial	01	1.1%
Idiosyncratic drugs	03	3.2%
Hakeem Medication intake	13	14.3%
Radiation exposure	02	2.1%
HBV	7	7.7%
HCV	3	3.2%
HIV	1	1.1%
Cause not found	56	61.5%
Hematological parameters	Mean	

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HB g/dl	6.22	±0.86
ANC (x 109/L)	0.56	±0.35
Platelet count (x 109/L)	60.4	±25.4
Reticulocyte count (%)	0.04	

Table 2: Clinical presentation, examination findings and laboratory investigations of all patients

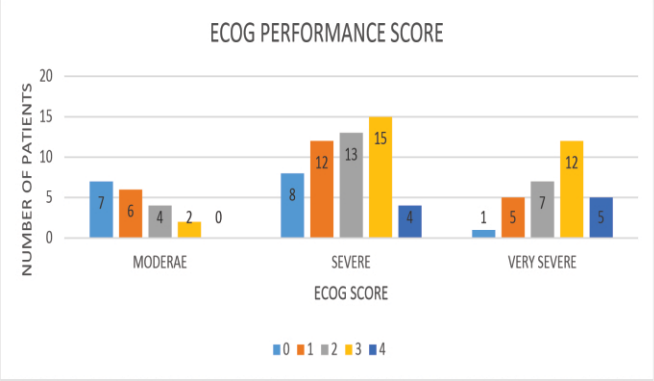

Figure 1: ECOG Performance Scale

The etiological factors were studied as causative factors of acquired aplastic anemia by asking detailed history from patients, duration of infection medication and exposure to causative agents. ECOG performance score was calculated for each patient at presentation, Figure 1. It was observed that the patients with severe aplastic anemia presented with high ECOG score as compared to moderate aplastic anemia patients who presented with lower ECOG score. The drugs taken by patients included penicillin, sulphonamides, antibiotics and allopurinol. Hakeem medication intake was also seen in 13 patients. Viral serology for hepatitis B and C virus infections was positive in 7 and 3 patients respectively, and one patient was diagnosed with HIV with ongoing antiviral therapy (HAART). No other etiological cause was seen in rest of the patients.

Variables		Outcome							
		Death		Spontaneous Remission		Remission		Relapse	
		Count	N %	Count	N %	Count	N %	Count	N %
Age group (years)	1-15	21	70.0	4	13.3	4	13.3	1	3.3
	15-30	25	54.3	6	13.0	12	26.1	3	6.5
	>30	14	93.3	1	6.7	0	0.0	0	0.0
Severity	Moderate	2	10.5	5	26.3	11	57.9	1	5.3
	Severe	29	69.0	5	11.9	5	11.9	3	7.1
	Very severe	29	96.7	1	3.3	0	0.0	0	0.0
Etiology	Drugs	2	22.2	2	22.2	5	55.6	0	0.0
	Infection	8	72.7	1	9.1	1	9.1	1	9.1
	Radiation	2	100.0	0	0.0	0	0.0	0	0.0
	Hakeem medication	9	69.2	1	7.7	2	15.4	1	7.7
	Cause not established	39	69.6	7	12.5	8	14.3	2	3.6

Table 3: Mortality rate of aplastic anemia studied with different parameters including age and severities of the disease

The treatment was given to patients according to institutional policy that included cyclosporin, ATG, MMF, Immunosuppressive therapy, anabolic steroids and supportive therapy according to the condition of the patients and criteria for remission and relapse was followed [10]. Only one of the patients underwent HSCT. Total 59 patients died causing a mortality rate of 64.8% in one-year follow-up. The mortality rate of aplastic anemia was studied with different parameters including age and severities of the disease are depicted in table 3. Highest mortality rate was seen in very severe aplastic anemia patients in which 29 out of 30 (96.7%) patients died even after aggressive treatment followed by severe aplastic anemia in which mortality rate was 69% (29 out of 42). Spontaneous remission criteria were achieved in 11 (12.1%) patients in whom complete hematological remission was achieved in average 3 months. However, in total complete remission was seen in 16 (17.6%) patients out of whom 4 patients relapsed. Around 12 patients were lost to follow up. Out of all the patients with remission, drugs and hepatitis virus infection were the main etiological factors. The Kaplan meiere survival curve was obtained for the included patients and was analyzed according to the severity of the disease Figure 2. The median time of death for patients with 12 weeks for very severe aplastic anemia, 26 weeks for sever aplastic anemia and 38 weeks for moderate aplastic anemia respectively.

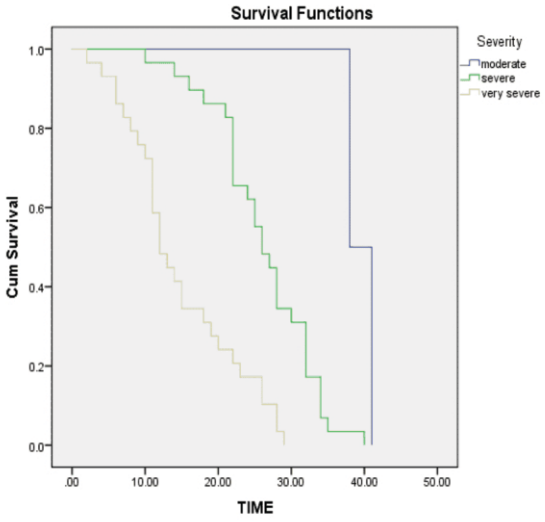

Figure 2: Kaplan Meiere Survival Curve

DISCUSSION

It was a cross sectional study conducted in the Hematology department Mayo Hospital, Lahore. The epidemiological data reveals that the disease is more prevalent in this area with male to female ratio 1.02:1. The male preponderance was also seen in a study conducted in India by Mahapatra et al., [11]. Recently in Pakistan a study of AA by Pervaiz Ahmed et al., was done, that depicted a high male to female ratio [12]. The mean age of all patients was calculated to be 30 years with a peak incidence seen among 15-30 years. The disease is reported in 5 individuals above the age of 60 years. The results were similar to a study by Parvez et al., [2]. The patients were divided into three groups according to the severity of aplastic anemia in which moderate aplastic anemia or non-severe aplastic anemia was

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present in 16 (17.5%) patients, severe aplastic anemia was seen in 48 (52.7%) patients and very severe aplastic anemia was seen in 27 (29.6%) patients in accordance to the study which showed the percentage of SAA is highest 45.2% in population of Pakistan. Several etiological factors in the development of acquired AA have been described in literature review. Most commonly chemicals including pesticide, infections and medical drugs are related with AA. In majority of the patients included in our study, the cause of aplastic anemia was undetermined. Idiopathic aplastic anemia is most likely due to immune activation leading bone marrow destruction. Hakeem medication and infections are among the most common causes found in our patients. Hepatitis B and C are very common in our region. The strongest association of aplastic anemia is seen with hepatitis B virus. The quackery and hakeem medication are still being taken in the suburban and rural areas of Pakistan. The major components of these medication are heavy metals and steroids. Out of 91 patients 13 patients had a history of taking hakeem medication for more than 6 months. Other drugs including antibacterial, antiepileptics, antimalarials or idiopathic drugs were taken by patients presented to us. Idiopathic causes were described as the most common etiological causes in development of aplastic anemia in various studies. Also, hepatitis B and C are considered to be responsible for 5 to 10% of AA cases [13]. Radiation exposure has also been linked to AA and in our study a total 3 patients had a history of radiation exposure. Two of the patients were working as technologist in radiology department. However, the dose and exact duration could not be determined. Exposure to ionizing radiation has been related to disruption of bone marrow architecture. Furthermore, there is a lack of awareness and following of protocols as depicted by studies conducted in Korea and Saudi Arabia [14,15]. The mortality rate is quite high when compared to the western countries. It can be attributed to multiple problems in third world countries like poverty, illiteracy, lost to follow up or lack of medical facilities. Definitive treatment with steroids and cyclosporine was taken by 5 (5%) patients of which 2 presented with very severe disease and died in first few days of treatment. Only one patient had bone marrow transplant done from CMH Rawalpindi and was living a healthy life till death. The highest mortality was seen in the patients who presented with very severe disease. Only one patient with VSAA showed spontaneous remission in our study, similar findings were seen in a study conducted in Agha Khan Hospital in Pakistan [16]. Medical drugs are considered important etiological factors in the development of AA and produce their effects by mediating immune response or generating a toxic reaction [17]. Drug induced AA has been described in nine patients in our study. However, the duration of medication varied among the patients. Treatment of aplastic anemia is indeed a challenge in developing countries. There is a delay in diagnosis and treatment. HSCT has better outcome as compared to immunosuppressive therapy with cyclosporin and ATG, but HSCT has certain limitation and cannot be done in every AA patient [18]. Similarly, a study done in India in 2015 by M Mahapatra described the treatment responses of the AA patients. According to their study, the response of cyclosporin alone and cyclosporin with androgen were 32.2% and 45.5% respectively. However, the rates of bone marrow transplant were better [19,20]. In our study only one patient underwent bone marrow transplant unfortunately. The low socioeconomic status and lack of medical facilities are the major reasons behind this. Furthermore, the established transplant units are also lacking, rendering these rather unapproachable to common people.

CONCLUSION

Aplastic anemia has life detrimental outcome with high mortality rate if left untreated. It is difficult to define the etiology of the disease especially when it comes to molecular levels. However, the management step is even more crucial for developing countries like Pakistan. There is a need to raise awareness on a larger platform so that better treatment facilities can be provided to the patients since it is one of the high incidences hematological disorder in Asian population

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