Hematological manifestations of aplastic anemia in patients with hypocellular marrow presenting in a tertiary care hospital in a developing country.

Maham Arshad1, Fahad Ahmed2, Ayesha Ellahi3, Aiza Saadia4, Javaid Usman5, Saleem Ahmed6

ABSTRACT... Objective: To see the hematological manifestations in patients with aplastic anemia presenting with hypocellular marrow. Study Design: Cross-sectional study. Setting: Department of Pathology, Pak Emirates Hospital, Rawalpindi. Period: January 2022 to June 2022. Material & Methods: Using non-probability consecutive sampling was done. All the patients were diagnosed of Aplastic anemia using standard established criteria. All the patients with hypocellular marrow without any granuloma, fibrosis or abnormal cells were included. A detailed history was taken from the patients, proforma was filled by consultants or trained doctors. Patients' interview was followed by Bone Marrow Examination. Statistical analysis was done using SPSS version 17.0. Descriptive statistics included frequency distribution of qualitative variables and calculation of mean with range for quantitative variables was done. Limitations were a lack of molecular testing to exclude the inherited bone marrow failure syndromes. Results: A total of 247 bone marrows were done in one year which were included in the study. Out of which ten patients had aplastic anemia and one patient had pure red cell aplasia which is the early form of aplastic anemia. Frequency of aplastic anemia in our study during the study period was found to be 4.45%. Minimum age of presentation is 5 years and maximum is 78 years with mean age of 43 years. Gender distribution is as 6 were males and 5 females out of total 11 aplastic anemia patients. In haematological manifestations 7 patients presented with history of bleeding from nose and gum. While rest of the 4 patients had fever, palpitations, breathing difficulties and generalized weakness. Conclusion: As we concluded that predisposing factors like younger age group and male predominance are leading toward genetic inheritance in aplastic anemia etiology especially among the South Asian population. The most common and foremost presentation in these patients was bleeding so aplastic anemia should be excluded when patients present with bleeding, fever and palpitations., Therefore, it is far better to early diagnosis and treat the patients to minimize the disease evolution.

Key words: Aplastic Anemia, Pure Red Cell Aplasia, Hypocellular Marrow.

INTRODUCTION
Aplastic anemia (AA) is signalized as pancytopenia on peripheral blood film which is explained as all three major cell lines in complete blood count (White blood cells, Haemoglobin and Platelets) are decreased. As bone marrow is the site of production of hematopoietic cells, in aplastic anemia the bone marrow examination shows hypocellular marrow with prominent fat spaces. The cellularity is decreased leading to reduced blood counts on the peripheral blood. As a concern worldwide aplastic anemia prevalence is relatively high in the Asian population as compared to rest of the world. The presentation of aplastic anemia is mostly in young age group and especially in the first three decades of life. The median age at which mostly patients present is about 15 years, then a second peak occurs around age 60 to 80 years. The presentation varies, in both inherited and acquired aplastic anemia. The comparison shows that acquired aplastic anemia patients as compared to inherited aplastic anemia commonly present at the age of 5 years.

On the whole the pathogenesis of aplastic anemia is idiopathic but they also necessitate immune mechanisms as well as genetic causes. Both of these are explained as when describing...
the immune destruction of hematopoietic stem cells and in genetic diseases both have inherited abnormal genes which include telomere disease and fanconi anemia. The underlying pathophysiology of idiopathic aplastic anemia (IAA) is described as by autoreactivity of human leukocyte antigen (HLA)-restricted T-cells against antigens which are presented by hematopoietic stem and progenitor cells (HSPCs). While further discussing when there is expansion of PIGA and HLA class I mutant HPSCs they have been linked to immune by T-cell mediated pressures. Although in idiopathic aplastic anemia as well there is also initiation by immunoeediting pressures and comes to a head with mechanisms of clonal evolution which is characterized by hits in immune recognition and response genes. The major important role in disease early onset is genetic predisposition and certain HLA alleles. They are responsible for early presentation. The following most important predisposing factors like pregnancy, viral hepatitis and immunological disorders may also lead to play a role in the disease development. Likewise the environmental factors, in comparison to genetic factors are believed to play predominant role in the disease presentation. There are wide spectrum of different viruses and chemicals which play an indigenous and important role in environmental causes that are involved in acquired aplastic anemia.

By definition pancytopenia means three major cell lines white blood cells, hemoglobin and platelets are below the normal ranges. As decrease white blood cells are associated with increased risk of infections, decrease haemoglobin leads to reduced oxygen carrying capacity in the blood and the presentation of the patient will be tiredness and shortness of breath, palpitations. On the other hand patients with decrease platelets will present with bleeding, bruises and epistaxis. As seen in these aplastic anemia patients platelets are the first initial parameter which is decreased than hemoglobin and white blood cells are affected. If these symptoms are missed and not diagnosed early which lead to delay in treatment of these patients can route to death.

In developing countries, like our country mostly patients visit to the doctor when disease has progressed. Due to strained resources and lack of availability of good quality laboratories. The diagnosis is delayed due to these reasons. The aim of this study is to see the hematological manifestations in patients with aplastic anemia presenting with hypocellular marrow in a tertiary care hospital. So that early diagnosis on initial symptoms and providing them early treatment help patients to live good quality and healthy life.

MATERIAL & METHODS
This cross-sectional study was conducted at Pak Emirates Hospital Rawalpindi which is an eleven hundred (1100) bedded hospital facility after approval from ethical committee (ERC/ID/143/25-02-2022). In this study we collected data from 247 patients coming to the tertiary care hospital using the non-probability consecutive sampling from January 2022 to June 2022. The sample size was calculated by WHO sample size calculator with confidence interval of 95% margin of error 5% and power of test 80%. The inclusion criteria was followed as all those patients diagnosed as aplastic anemia using standard established criteria, with hypocellular marrow without any granuloma, fibrosis or abnormal cells were included in the study. A detailed history was taken from the patients, proforma was filled by consultants or trained doctors. Which is attached including these parameters like patients age, gender, signs and symptoms at the time of presentation. Patients’ interview was followed by bone marrow examination including complete blood counts. Statistical analysis was done using SPSS version 17.0. In descriptive statistics, for gender distribution percentage was calculated, for age mean was calculated with minimum and maximum age at presentation. Hematological parameters of complete blood counts and bone marrow were noted. In patients with aplastic anemia the most common symptoms and which are less likely were also noted and percentage was calculated. There are limitations in the study as lack of molecular testing to exclude the inherited bone marrow failure syndromes.
Inclusion Criteria
Bone marrow cellularity <25%<sup>18</sup>
There must be at least two of the following

Haemoglobin <10g/dl (Reticulocyte <20x10<sup>9</sup>/l)

Neutrophil Count
Non severe <1.5x10<sup>9</sup>/l
Severe <0.5x10<sup>9</sup>/l
Very severe <0.2x10<sup>9</sup>/l

Platelet Count
Non severe <50x10<sup>9</sup>/l
Severe <20x10<sup>9</sup>/l

Exclusion Criteria
Patients with hypocellular marrow with any granuloma, fibrosis or abnormal cells were excluded from the study

RESULTS
A total of 247 bone marrows were done in six months which were included in the study. Out of which ten patients had aplastic anemia and one patient had pure red cell aplasia which is the early form of aplastic anemia. Frequency of aplastic anemia in our study during the study period was found to be 4.45%. Minimum age of presentation is 5 years and maximum is 78 years with mean age of 43 years. Gender distribution included 6 males and 5 females out of total 11 aplastic anemia patients. In haematological manifestations 7 patients presented with history of bleeding from nose and gum. While rest of the 4 patients had fever, palpitations, breathing difficulties and generalized weakness.

Blood Counts of Patients Diagnosed with Aplastic Anemia

<table>
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<tr>
<th>Hemoglobin gm/dl</th>
<th>Absolute Neutrophil Count %</th>
<th>Retic Count 10&lt;sup&gt;9&lt;/sup&gt;/l</th>
<th>Platelets Count 10&lt;sup&gt;9&lt;/sup&gt;/l</th>
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<tbody>
<tr>
<td>8.8</td>
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<td>0.1</td>
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<tr>
<td>8</td>
<td>0.32</td>
<td>&lt; 0.5</td>
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<td>7.7</td>
<td>1.8</td>
<td>2.1</td>
<td>80</td>
</tr>
<tr>
<td>7.7</td>
<td>3.8</td>
<td>&lt; 0.5</td>
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<tr>
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<td>0.5</td>
<td>&lt; 0.5</td>
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<tr>
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DISCUSSION
Aplastic anemia is the archetype bone marrow failure syndrome and can be classified as either acquired or inherited. As a concern in their pathophysiology the underlying germline mutations may play a role in inherited aplastic anemia. While in comparison acquired aplastic anemia is suspected to result from cytotoxic T cell mediated immune attack on hematopoietic and progenitor cells.<sup>19</sup> Aplastic anemia manifests as cytopenia’s with a hypocellular bone marrow. The percentage of hypocellularity in bone marrow lead to decrease blood counts which appear as clinical symptoms in patients and further consequent clinical sequelae. In our study we wanted to see that if patients are diagnosed at early stage with early signs and symptoms and treated this can prevent disease evolution.
In our study there was a wide variation in the age group of the presenting patients as a minimum child of 5 years and an maxim elderly of 78 years. The male predominance is noted in data we collected from patients. The early presentation point toward genetic factors in aplastic anemia etiology among the South Asian population. In clinical presentation of the patients the most important symptom was bleeding from the nose and gum. Less markedly were fever, palpitations, breathing difficulties and generalized weakness. As studies have shown that mostly it is the platelet count which is the first parameter to be affected, the decrease platelet count in aplastic anemia patients is responsible for bleeding.\textsuperscript{20} Then other parameters like white blood cells and hemoglobin are affected they are the underline causes for fever and palpitations.\textsuperscript{21} In our resource strained underdeveloped country when patients present with these symptoms, they should be scrutinized for aplastic anemia. The foremost and important initial investigation to be done is complete blood counts. Which will show further that if they are below the reference range than bone marrow examination becomes necessary to exclude aplastic anemia. If disease is diagnosed in initial stage early treatment can prevent disease progress and complications can be avoided.\textsuperscript{22} To control disease early while availing less resources is the best option in our country as compare to cure with complications and to avoid being financially overburdened.

**LIMITATION**

Due to lack of funding and adequate human resource at the center. We acknowledge that molecular testing (PCR) and chromosomal breakage analysis is not done so the possibility of inherited bone marrow failure syndromes on the basis of molecular markers cannot be confirmed.

**CONCLUSION**

Aplastic anemia which has been classified in the life threatening bone marrow failure disorder having high mortality due to complications and if it remains untreated. The presentation of the symptoms in the younger age group, male predominance point toward genetic factors involved in the etiology of aplastic anemia especially among the South Asian population.

As with the development of research in aplastic anemia pathophysiology it is analyzed that hematopoietic stem cell transplantation is the ultimate treatment and an opportunity to cure but it also has its pros and cons. It is an expensive procedure and associated with 20% mortality. Immunosuppressive therapy is the next option of choice. As the majority of patients also do not fulfil the pre requests for hematopoietic stem cell transplant. In our low socioeconomic underdeveloped country, the diagnosing of these patients with early clinical manifestations is the utmost practical approach. In our study the most common presentation in these patients was bleeding so aplastic anemia should be ruled out when patients present with bleeding, fever and palpitations. So that the early diagnosis and timely providing them with good quality treatment can minimize the disease evolution.

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**REFERENCES**


**AUTHORSHIP AND CONTRIBUTION DECLARATION**

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<tr>
<th>No.</th>
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<th>Contribution to the paper</th>
<th>Author(s) Signature</th>
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