

ETIOLOGICAL SPECTRUM OF CYTOPENIAS IN ADULT PAKISTANI POPULATION: A SINGLE CENTRE EXPERIENCE

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ABSTRACT

OBJECTIVE: To determine the frequency and etiology of various cytopenias in adult patients presenting to the medical unit of Kuwait Teaching Hospital, Peshawar, Pakistan.

METHODS: The study was conducted from January 2015 till June 2016, on 115 patients presenting to medical unit of Kuwait Teaching Hospital, Peshawar, Pakistan. Out of these 62 (54%) were males and 53 (46%) were females. Patients above 15 years of age having various cytopenias on complete blood count were included in the study. This was followed by peripheral smear examination. Bone marrow aspiration and trephine biopsy was performed where indicated. The data was further stratified into pancytopenia, thrombocytopenia and anemia and their respective causes with frequencies were calculated.

RESULTS: Pancytopenia was detected in 66/115 (57.4%) cases. Megaloblastic anemia (n=29/66; 43.9%), aplastic anemia (n=10/66; 15.2%) and acute leukemia (n=10/66; 15.2%) were the major causes of pancytopenia. Other causes of pancytopenia included multiple myeloma (n=9/66; 13.6%), disseminated intravascular coagulation (n=4/66; 6.1%), myelo-suppression (n=2/66; 3%) and myelodysplasia (n=2/66; 3%). Thrombocytopenia was diagnosed in 44/115 (38.3%) cases. Vivax malaria (n=19/44; 43.2%), idiopathic thrombocytopenic purpura (n=11/44; 25%), hypersplenism (n=7/44; 15.9%) and dengue hemorrhagic fever (n=4/44; 9.1%) were the main causes of thrombocytopenia. Iron deficiency anemia was observed in 5/115 (4.3%) cases, all were females.

CONCLUSION: Pancytopenia and thrombocytopenia are the commonest cytopenias encountered in adult patients presenting to a medical unit in our hospital. Megaloblastic anemia is the commonest cause of pancytopenia followed by aplastic anemia and leukemia. In thrombocytopenia, vivax malaria and idiopathic thrombocytopenic purpura were the commonest causes.

KEY WORDS: Cytopenias (Non-MeSH); Thrombocytopenia (MeSH); Pancytopenia (MeSH); Anemia (MeSH); Peripheral smear (Non-MeSH); Bone marrow (MeSH); Trephine biopsy (Non-MeSH); Biopsy (MeSH); Anemia, Iron-Deficiency (MeSH).

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For the purpose of description, cytopenias are classified into two groups. The first group is cytopenias with a cellular marrow and it includes myelofibrosis, myelodysplasia, paroxysmal nocturnal hemoglobinuria (PNH), aleukemic leukemia, hairy cell leukemia, folate or vitamin B₁₂ deficiency, hypersplenism, tuberculosis, overwhelming infections and systemic lupus erythematosus (SLE). Some immune mechanisms, for instance autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura (ITP) may also be at play. Another important finding is malaria, which is still considered to be the commonest cause of acquired thrombocytopenia.³

The second group is cytopenias with a hypo-cellular bone marrow and that includes pancytopenia as the commonest presentation followed by some rare leukemias and lymphomas. From a clinical perspective the bone marrow failure syndromes deserve special attention because they can be missed in routine testing. Peripheral smear examination along with bone marrow aspiration and trephine biopsy can point out the diagnosis in a timely and effective manner. The patients treated in time often have a better clinical outcome.⁵ Many studies have been performed in the past to find the causative agents and mechanisms behind various cytopenias worldwide.^{4,5}

Steady rise in the number of adult patients with hematological abnormalities have been observed over the past

INTRODUCTION

Cytopenias are an important health issue in third world countries and frequently encountered in the medical units.¹ Patients with these hematological disorders presents with prolonged

fever, increased pallor and tendency to bleed. The etiology of cytopenias is varied and can either be related to a bone marrow dysfunction or to a peripheral destruction and in each case the diagnostic approach and treatment options are entirely different.²

few years, especially after the Afghan war.⁶ Whether it reflects changes in the genetic constitution and climate or simply an aftermath of war, requires further probing. Studies on the pattern and frequency of cytopenias in adult population of Pakistan are limited and a few studies were conducted in pediatric age group.⁷⁻¹⁰ The aim of our study was to identify the causes of various cytopenias in adults in a simple and cost effective way. The results of the study will enhance our knowledge regarding the local patterns of the disease which can be used to help the patients more effectively.

METHODS

This prospective study was undertaken in the Department of Medicine, Kuwait Teaching Hospital, Peshawar, Pakistan from January 2015 till June 2016, after taking approval from the institutional review board of the Prime Foundation, Peshawar, Pakistan. Informed consent was obtained from all the study participants. A total of 115 cases were included in the study out of which 62 were males and 53 were females. Patients above 15 years of age having various complaints were advised complete blood count (CBC) and those having decrease in cell counts were invited to participate in the study.

After taking a detailed history and performing physical examination, routine investigations i.e. CBC, liver function tests, renal function tests, random blood sugar and urinalysis were performed. Patients having a decrease in one or more of the cell lines on CBC were subjected to peripheral smear examination. Bone marrow aspiration was performed for the following indications: diagnosis and staging of lymphoproliferative and myeloproliferative disorders, plasma cell dyscrasias, evaluation of thrombocytopenia, anemia and infiltrative disorders.

Blood samples for CBC were collected in tubes having K₂ EDTA for 3 ml blood (ATLAS-LABOVAC, Italiano) under aseptic precautions and analyzed using Abbott Cell Dyne Ruby Analyzer. All patients presenting with hemoglobin (Hb) less than 10.0g/dl, platelet count less than 150,000/dl and total leukocyte count (TLC) less than 4000/dl were included in the study through non

probability convenience sampling. Peripheral smear was stained using Giemsa stain (Merck) and supra vital stain for reticulocytes (Dia 3 Chem Lab). Bone marrow aspiration was performed, when required, using disposable spinal needle 16G (Fine Core Dr. Japan) and the slides were stained using Giemsa and Perl's stain (Merck). Bone marrow trephine biopsy was taken using disposable 11G needle (Tic. San. Ltd. STi, Turkey). Biopsy samples were preserved in 10% formalin and sent to histopathology division of Excel Lab, Islamabad. The tissues were decalcified and embedded in paraffin. Slides were prepared and stained with Hematoxyline & Eosin (Merck). Slides were examined and reported by consultant hematologist.

Demographics of the patients, clinical features and results were recorded on a specially designed proforma. The data was further stratified into pancytopenia, thrombocytopenia and anemia. The causes and frequencies in all the groups were calculated. The results obtained were organized in Microsoft Excel 2007 and analyzed using SPSS version 20.

RESULTS

Out of 115 patients who participated in the study, 62 (54%) were males and 53 (46%) were females. They were further divided into three groups: patients below 30 years of age were 46 (40%), between 30 and 60 years were 54 (47%) and above 60 years of age were 15 (13%).

Pancytopenia was detected in 66/115 (57.4%) cases. Megaloblastic anemia (n=29/66; 43.9%), aplastic anemia (n=10/66; 15.2%) and acute leukemia (n=10/66; 15.2%) were the major causes of pancytopenia. (Table I).

Thrombocytopenia was diagnosed in 44/115 (38.3%) cases. Vivax malaria (n=19/44; 43.2%), idiopathic thrombocytopenic purpura (n=11/44; 25%), hypersplenism (n=7/44; 15.9%) and dengue hemorrhagic fever (n=4/44; 9.1%) were the main causes of thrombocytopenia (Table II). Iron deficiency anemia was observed in 5/115 (4.3%) cases, all were females.

DISCUSSION

Peripheral smear is an important clinical test which is very helpful in establishing

causes of various cytopenias detected through CBC. Among them thrombocytopenia and pancytopenia are important and they should be suspected in any febrile patient with bleeding tendency.¹¹ The etiology of cytopenias is quite varied and suggests some interesting epidemiological patterns. Our results showed that 57.4% of the patients presented with pancytopenia, which is consistent with other studies performed in the similar settings.^{2-4,8} The commonest cause of the pancytopenia was megaloblastic anemia 44.1% which is also consistent with the previous findings.^{2-4,8} As many of these patients came from a low socioeconomic background hence factors like diet, multiparity and poor hygiene might be at play.¹² Interestingly a large number 46.9% were due to a more serious abnormalities of the bone marrow. Aplastic anemia and leukemia comprised of 15.2% each. Multiple myeloma, another malignancy involving the bone marrow, was detected in 13.6% cases.

Among the patients with leukemia 60% had acute myeloid leukemia (AML-M2 and M3) variety and 40% had acute lymphoblastic leukemia (ALL- L1 and L2) as a diagnosis. Myelodysplasia was diagnosed in two patients. In contrast to other studies there has been an increase in these cases recently.^{2,8,12,13} Disseminated intravascular coagulation (DIC) as a cause of pancytopenia was detected in 6% of the pancytopenic patients, which was also a new finding as compared to previous studies.¹⁴ Bone marrow suppression due to interferon and ribavirin therapy was diagnosed in 3% cases. Iron deficiency anemia was found to be the cause in all the cases of anemia which were 5 (4.3%). All these patients were females.

Thrombocytopenia alone was diagnosed in 38.2% cases. As stated earlier, there has been not much work done in the adult population to ascertain the etiology of thrombocytopenia. However, a study done in the same population found malaria as a common cause of thrombocytopenia which was consistent with our study too.¹⁴ Vivax malaria was found to be a cause in 43.2% of these patients and falciparum malaria in 2.3%. A new development, however, was a recent epidemic of

dengue hemorrhagic fever which resulted in severe thrombocytopenia in 9% of these patients. ITP was diagnosed in 25% of these adult patients too which is otherwise a common cause in pediatric population. Hypersplenism was next in frequency 16% among thrombocytopenic patients. All these cases were secondary to chronic liver disease resulting in splenomegaly. Interestingly one of the patients had thrombocytopenia rather than thrombocytosis along with high TLC later confirmed as a case of chronic myeloid leukemia. Evan's syndrome secondary to chronic lymphocytic leukemia (CLL) resulting in thrombocytopenia was diagnosed in one patient only.

In comparison with the international studies many features of our study are consistent with their findings as well. Megaloblastic anemia was the most frequent diagnosis in our study as well as in other studies.^{15,16} The higher numbers of megaloblastic anemia seems to reflect a higher prevalence of deficiency of vitamin B₁₂ and folate. Further studies are warranted in this direction to ascertain the factors leading to this pattern especially in adult males as they were mainly affected.

In the present study, hematological malignancy as a cause of pancytopenia was found in an alarmingly large number. In the study by Jha A. et al. the most common condition was acute leukemia. Plasma cell myeloma, myelodysplastic syndrome (MDS) and non-Hodgkin lymphoma (NHL) were the other three hematological malignancies in adults.³ This was also a finding in our study in which after megaloblastic anemia, malignancies and MDS are the main cause of pancytopenia. There was a small number patients presenting with DIC as a cause. This was a new finding not found in previous studies and might suggest a lack of proper evaluation and treatment facility at less developed areas of our province.

Compared to other international studies with more or less similar demographics, hematological malignancies were not in significant numbers. In one of the study by Kumar, et al. no acute leukemia was detected.¹⁷ Similarly in the studies by Khodke, et

TABLE I: FREQUENCY DISTRIBUTION OF PANCYTOPENIAS (n=66)

Diagnosis	Males	Females	Total
Megaloblastic anemia	20 (30.4%)	9 (13.7%)	29 (43.9%)
Leukemia	7 (10.6%)	3 (4.6%)	10 (15.2%)
Aplastic anemia	6 (9%)	4 (6%)	10 (15.2%)
Multiple myeloma	4 (6%)	5 (7.7%)	9 (13.6%)
Disseminated intravascular coagulation	2 (3%)	2 (3%)	4 (6.1%)
Myelodysplasia	2 (3%)	0	2 (3%)
Drug induced myelosuppression	2 (3%)	0	2 (3%)
Total	43 (65%)	23 (35%)	66 (100%)

TABLE II: FREQUENCY DISTRIBUTION OF THROMBOCYTOPENIAS (n=44)

Diagnosis	Males	Females	Total
Vivax malaria	8 (18.2%)	11 (25%)	19 (43.2%)
Idiopathic thrombocytopenic purpura	2 (4.5%)	9 (20.4%)	11 (25%)
Hypersplenism	2 (4.5%)	5 (11.4%)	7 (15.9%)
Dengue hemorrhagic fever	4 (9.1%)	0	4 (9.1%)
Falciparum malaria	1 (2.3%)	0	1 (2.3%)
Evans syndrome	1 (2.3%)	0	1 (2.3%)
Chronic myeloid leukemia	1 (2.3%)	0	1 (2.3%)
Total	19 (43.2%)	25 (56.8%)	44 (100%)

al.¹⁸ and Tilak, et al.¹⁵ one case of AML was detected as a cause of pancytopenia. Nevertheless, in the study of Bashawri the main indication for bone marrow examination in cases of pancytopenia was investigation of acute leukemia.¹⁹ Acute leukemia was the third common cause of pancytopenia in the study of Varma and Dash.²⁰ Similarly, in the study by Savage, et al.²¹ in Zimbabwe, acute leukemia constituted the third most common cause of pancytopenia. In their study, patients with hypo-plastic anemia and acute leukemia were usually children, whereas those with megaloblastic anemia were adults, the later finding AML being in accordance with our study. ALL was the commonest acute leukemia in the pediatric age while AML was the commonest in adults in most of these studies. Only three cases of ALL (two cases of ALL-L2 and one case of ALL-L1) were seen in adults. In our study the ALL variety of leukemia was found in adults as well in contrast to the well-established finding that ALL is common in children. ALL-L1 was the most common type of ALL while AML-M2 was the most common type of AML, and most of them were seen in adults similar to our findings. This finding along with an increased number of aplastic anemia and multiple myeloma is an important feature of this study. In light of the changing demographics of our province and the environmental changes secondary to a war struck area further studies

are required to ascertain the true nature and magnitude of this problem.

Equally important are the high number of malaria and dengue fever causing symptomatic thrombocytopenia along with chronic liver disease and hypersplenism. This makes the current efforts to control these endemic diseases ineffective and require more efficient means.

This study was performed on a relatively smaller number of patients with more or less similar demographic and genetic profile. There are many genetic factors having important effect on the bone marrow. A large scale study with a variant genetic pool and larger sample size can fully assess the impact of genes on these cytopenias.

CONCLUSION

Pancytopenia and thrombocytopenia are the commonest cytopenias encountered in adult patients presenting to a medical unit in our hospital. Megaloblastic anemia is the commonest cause of pancytopenia followed by aplastic anemia, leukemia and multiple myeloma in respective order. In thrombocytopenia, vivax malaria, ITP and hypersplenism were the commonest causes. Alarmingly large numbers of bone marrow malignancies require further studies to find the causes behind it. Furthermore, a larger study is required to evaluate the incidence of thrombocytopenia in malaria.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

SM: Acquisition, analysis & interpretation of data, drafting the manuscript, final approval of the version to be published

FS & SM: Acquisition of data, drafting the manuscript, final approval of the version to be published

IAS: Concept & study design, critical review, final approval of the version to be published

AZ: Acquisition of data, final approval of the version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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