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ETIOLOGY AND FREQUENCY OF VARIOUS CYTOPENIAS PRESENTING IN MEDICAL UNIT ON THE BASIS OF PERIPHERAL SMEAR AND BONE MARROW EXAMINATION Saima Mehboob1, Faridullah Shah2, Sardar Muhammad3, Iftikhar Ali Shah,4 Akhtar Zarin5 Corresponding author DR. Saima Mehboob MBBS, FCPS Medicine Assistant Professor drsaima758@gmail.com Cell: +92-333-9396964 1, 2, 4 Department of Medicine Kuwait Teaching Hospital Peshawar Medical College Peshawar, KPK, Pakistan. DR. Faridullah Shah MBBS, FCPS Medicine Associate Professor DR. Sardar Muhammad MBBS, DOMS, M Phil Assistant Professor 3, 5 Department of Pathology Peshawar Medical College drsmak55@gmail.com Cell: +923458881954 DR. Iftikhar Ali Shah MBBS, FCPS, MRCP (UK) Professor and Head Department of Medicine DR. Akhtar Zarin Khattak MBBS, Dip in Path (AFPGMI), FCPS(Hem) Professor of Haematology Abstract: Introduction: Cytopenias are an important problem frequently encountered in medical units. The etiology is varied and little is known about the exact frequencies of various etiological agents in the adults.

3**In our country studies have been conducted** mainly on **the**

pediatric population. A steady rise in the number of adult patients with hematological abnormalities has been observed.

1**The aim of** the **study was to identify the** frequencies and **causes of** various Cytopenias **in**

adults in a simple and cost effective way. Objective: To determine the frequency and etiology of various Cytopenias on the basis of peripheral smear and bone marrow examination. Study design: Descriptive case series. Setting: Kuwait teaching Hospital Peshawar, Department of Medicine. Duration of study: The study was performed from 1st January 2015till 1st June 2016 Subjects and methods: After approval from the hospital ethical and research committee, the study was carried out on 115 patients above age 15 presenting to medical unit. They were recruited through non probability convenience sampling. Out of these 62(54%) were males and 53 (46%) were females with various Cytopenias on routine blood testing. They were further divided into three groups. Patients below 30 years were 46(40%), between 30 and 60 years were 56 (47%), and above 60 years were 15(13%). Peripheral smear examination was done next and bone marrow biopsy was performed where indicated. Results: The data was further stratified into Pancytopenia, thrombocytopenia and anemia and their respective causes with frequencies were calculated. Out of 115 cases 66 (57.3%) presented with pancytopenia. Among them Megaloblastic anemia comprised of 29 (25.2%) of the cases. Aplastic anemia was found in 10 (8.6%) of the cases and a similar percentage 10 (8.6%) of patients had multiple myeloma.4 (3.4%) had disseminated intravascular coagulation as a cause. 2 (1.7%) had drug induced myelosuppression and another 2 (1.7 %) had myelodysplasia. Thrombocytopenia only was detected in 44 (38.2%) while 5 (3.4%) cases presented with Iron deficiency anemia. Conclusion: Peripheral smear and bone marrow examination are important diagnostic tools for detecting Cytopenias. Pancytopenia and thrombocytopenia were the commonest Cytopenias encountered in adults.

4**Megaloblastic anemia** is **the** commonest **cause** of **pancytopenia followed by**

aplastic anemia,

leukemia and multiple myeloma. In thrombocytopenia, Vivax malaria and dengue fever were the commonest causes followed by ITP and hypersplenism. Key words: Cytopenias, .peripheral smear , bone marrow Introduction: Cytopenias are an important health issue in third world countries and frequently encountered in the medical units1. The etiology is varied and little is known about the exact frequencies of various etiological agents in our setup as most of these studies were performed on the pediatric population not the adults 2,3. These Cytopenias can either be related to a bone marrow dysfunction or related to a peripheral destruction and in each case the diagnostic approach and treatment options are entirely different4. 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, PNH (paroxysmal nocturnal heamoglobinuria), leukemic leukemia, hairy cell leukemia, folate or B12 deficiency, hypersplenism, tuberculosis, overwhelming infections and SLE. Some immune mechanism like autoimmune hemolytic anemia, ITP may also be at play. Also Infection like Malaria which is still considered the commonest cause of acquired thrombocytopenia5. 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 are often overlooked in routine testing. Peripheral smear examination along with bone marrow aspiration and trephine when performed where indicated, can point out the diagnosis in a timely and effective manner. The patients treated in time often have a better clinical outcome5. Many studies have been performed in the past to find the causative agents and mechanisms behind various Cytopenias worldwide6,7. In our country such studies have been performed mainly on the pediatric population2, 3. Steady rise in the number of adult patients with hematological abnormalities have been observed over the past few years, especially after the afghan war 8, 9. Whether it reflects changes in the genetic constitution and climate or simply an aftermath of war, requires further probing.

1**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. Material and Methods:

This prospective study was undertaken in the department of medicine Kuwait teaching hospital Peshawar from January 2015 till June 2016, after taking approval from the ethical and research committee. A total number of 115 cases above 15 years of age were included in the study out of which 62 were males and 53 were females. They were divided into three groups. Patients below 30 years were 46(40%), between 30 and 60 years were 56 (47%), and above 60 years were 15(13%).All patients presenting with

5Hb less than 10. 0g /dl, platelet count less than

150,000/dl, and TLC less 4000/dl were included in the study through non probability convenience sampling. After history and physical examination baseline investigations were done first, later Peripheral blood smears were examined and in the light of the results, bone marrow examination was done where indicated. Results: The data was further stratified into pancytopenia, thrombocytopenia and anemia with their respective causes &frequencies were calculated. Pancytopenia was detected in 66 out of 115(57.3%) cases. Among them Megaloblastic anemia comprised of 29 (25.2%) of the cases. Aplastic anemia was found in 10 (8.6%) of the cases and a similar percentage 10 (8.6%) of patients had multiple myeloma.4 (3.4%) had disseminated intravascular coagulation as a cause. Drug induced myelosuppression was detected in 2 (1.7%) and another 2 (1.7 %) had myelodysplasia. Out of the total 115 cases, 44(38.2%) presented to us with thrombocytopenia only. Vivax malaria was found to be a cause in 19 (16.5%) of these patients and Falciparum malaria in 1(0.9%). 4(3.4 %) of them had dengue hemorrhagic fever. Hypersplenism was the cause in 7(6.0%) of the patients. Idiopathic thrombocytopenic purpura was found in 11 (9.5 %) of them whereas Evan's syndrome and chronic myeloid leukemia constituted 1(0.9 %) each. Iron deficiency anemia was found to be the cause in all the cases of anemia which were 5(4.3/%) of the patients. Age-wise distribution: 60 54 50 46 40 30 20 15 0 Below 30 30-60 Above 60 Gender-wise distribution: 64 62 62 60 58 56 54 53 52 50 48 Female Male Thrombocytopenia: 38.2% Diagnosis Frequency Percentage Malaria (Plasmodium Vivax) 19 16.5% Malaria (Plasmodium Falciparum) 1 0.9% Dengue Hemorrhagic fever 4 3.4% Hypersplenism 7 6.0% Idiopathic Thrombocytopenic Purpura 11 9.5% Evan's syndrome

81 0.9% Chronic Myeloid Leukemia 1 0.9%

Pancytopenia: 57.39% Diagnosis Frequency Percentage Megaloblastic anemia 29 25.2% Myelodysplasia 2 1.7% Leukemia 10 8.6% Myeloma 9 7.8% Aplastic anemia 10 8.6% Drug induced myelosuppression 2 1.7% Disseminated Intravascular Coagulation 4 3.4% Anemia: 4.34% Diagnosis Frequency Percentage Iron deficiency anemia 5 4.3% Discussion: Peripheral smear is an important clinical test which can pick a variety of abnormalities notably the Cytopenias. Among them thrombocytopenia and Pancytopenia are the most important and they should be suspected in any febrile patient with bleeding tendency10. The etiology of Cytopenias is quite varied and suggests some interesting epidemiological patterns. Results showed that 57.39% of the patients presented with Pancytopenia which is consistent with other studies performed in the similar settings.

5**The commonest cause of** the **Pancytopenia was Megaloblastic anemia** (25.2%) **which**

is also consistent with the previous findings. As many of these patients came from a poor background hence factors like diet, multiparty and poor hygiene might be at play11. Interestingly enough a large number (31 out of 66) were due to a more serious abnormality of the bone marrow. So aplastic anemia and leukemia comprised of (10) 8.6% each. Furthermore 7.8% presented with multiple myeloma, another malignancy involving the bone marrow. Among the patients with leukemia 6 had Acute Myeloid Leukemia (AML-M2 and M3) variety and 4 had Acute Lymphoblastic Leukemia (ALL- L1 and L2) as a diagnosis. Myelodysplasia was diagnosed in 2 (1.7%) patients. In contrast to other studies there has been an increase in these cases recently 3, 4, 10. 11. Disseminated intravascular coagulation (DIC) as a cause of pancytopenia was detected in 4(3.4%) of these patients, which was also a new finding as compared to previous studies12. Bone marrow suppression due to Interferon and ribivirin therapy was diagnosed in 2(1.7%) cases. Iron deficiency anemia was found to be the cause in all the cases of anemia which were 5(4.3/%) of the patients. The other subset were the patients presenting with thrombocytopenia alone and they comprised of (38.2%) of the total patients. As stated earlier, there has been not much work done in the adult population to ascertain the etiology of thrombocytopenia. However one study done in the same population enlists malaria as a common cause of thrombocytopenia12 which was consistent with our study too. Vivax malaria was found to be a cause in 19 (16.5%) of these patients and Falciparum malaria in 1(0.9%). A new development however was a recent epidemic of Dengue hemorrhagic fever which resulted in severe thrombocytopenia in 4 (3.4%) of

these patients. Idiopathic thrombocytopenic purpura (ITP) was diagnosed in 11(9.5%) of these adult patients too which is otherwise a common cause in pediatric population. Hypersplenism was next in frequency 7 (6%). All these cases were secondary to chronic liver disease resulting in splenomegaly. Interestingly enough 1 (o.9%) of the patients had thrombocytopenia rather than thrombocytosis along with high TLC later confirmed as a case of chronic myeloid leukemia. 1 patient has Evan's syndrome secondary to CLL resulting in thrombocytopenia. 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.13, 14 The higher numbers

1**of Megaloblastic** anemia **seem to reflect** a **higher prevalence of deficiency**

of vit 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.et al the most common condition was acute leukemia. Plasma cell myeloma, Myelo Dysplastic Syndrome (MDS) and Non Hodgkin Lymphoma (NHL) were the other three hematological malignancies in adults15. 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

2**Kumar et al no acute leukemia**

was detected16. Similarly, in the studies by Khodke et al 17 and

2**Tilak et al** 13one **case of** AML **was detected as a cause** of **Pancytopenia.**

Nevertheless, in **the** study of Bashawri **the**

main

> 9**indication for bone marrow examination in** cases **of** Pancytopenia was investigation **of**

acute leukemia18.

> 6**Acute leukemia was the third common cause of Pancytopenia in the study of Varma and**

Dash19. Similarly, in the study of Savage et al20 in Zimbabwe,

> 2**acute leukemia constituted** the **third most common cause of Pancytopenia. In** their **study,**

patients with hypo plastic

> 7**anemia and acute leukemia were usually children, whereas those with Megaloblastic anemia were adults,**

the later finding is 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

> 3**(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 stricken 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 CLD and hypersplenism. This makes the current efforts to control these endemic diseases ineffective and require more efficient means. Conclusion: Peripheral smear and bone marrow examination are important diagnostic tools for detecting Cytopenias. Pancytopenia and thrombocytopenia were the commonest Cytopenias encountered in adults.

4**Megaloblastic anemia** is **the** commonest **cause** of **Pancytopenia followed by aplastic anemia,**

leukemia and multiple myeloma. In thrombocytopenia, Vivax malaria and dengue fever were the commonest causes followed by ITP and hypersplenism. 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 malari