ETIOLOGY AND FREQUENCY OF VARIOUS CYTOPENIAS PRESENTING IN MEDICAL UNIT ON THE BASIS OF PERIPHERAL SMEAR AND BONE MARROW EXAMINATION

by Sardar Muhammad

FILE	17399-67498-1-RV.DOCX (47.18K)		
TIME SUBMITTED	06-FEB-2017 04:30PM	WORD COUNT	2888
SUBMISSION ID	767139687	CHARACTER COUNT	16139

ETIOLOGY AND FREQUENCY OF VARIOUS CYTOPENIAS PRESENTING IN MEDICAL UNIT ON THE BASIS OF PERIPHERAL SMEAR AND BONE MARROW EXAMINATION

Saima Mehboob[1], Faridullah Shah[2], Sardar Muhammad[3], Iftikhar Ali Shah,[4] Akhtar Zarin[5]

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 Hematology

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. 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. 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 2015 to 1st June 2016

Subjects and methods: After approval from the Institutional Review Board of the Prime Foundation Pakistan, 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. The samples were processed in Pathology Laboratory of Kuwait Teaching Hospital Peshawar. Bone Marrow aspiration was performed by Professor Akhtar Zarin.

Results: The data was further stratified into Pancytopenia, thrombocytopenia and anemia and their respective causes with 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%) had multiple myeloma. Disseminated intravascular coagulation as a cause was diagnosed in 4 (3.4%). Drug induced myelo suppression was found in 2 (1.7%) 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. 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 units[1]. 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 to a peripheral destruction and in each case the diagnostic approach and treatment options are entirely different[4].

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 and Idiopathic Thrombocytopenic Purpura (ITP) may also be at play. Also Infection like Malaria which is still considered the commonest cause of acquired thrombocytopenia[5].

The second group is Cytopenias with a hypo-cellular bone marrow and that includes Pancytopenia as the commonest presentation followed by some rare leukemia's 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 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[6, 7]. In our country such studies have been performed mainly on the pediatric population[2, 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. 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 Institutional Review Board of the Prime Foundation Pakistan. 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%).

Samples for baseline investigations were collected under aseptic precautions and analyzed using Abbott Cell Dyne Ruby Analyzer. All patients presenting with Hb less than 10.0g/dl, platelet count less than 150,000/dl, and TLC less than 4000/dl were included in the study through non probability convenience sampling. Peripheral smear was stained using Giemsa and Reticulocyte stain. Bone marrow aspiration was performed, when required, using disposable spinal needle 16G and the slides were stained using Giemsa and Perl's stain. Bone marrow trephine biopsy was taken using disposable Turkish needle. Biopsy samples were processed in Histopathology division of Excel Lab Islam Abad. The blocks received back and the slides prepared and stained were examined and reported by Professor Akhtar Zarin, consultant Hematologist.

Results:

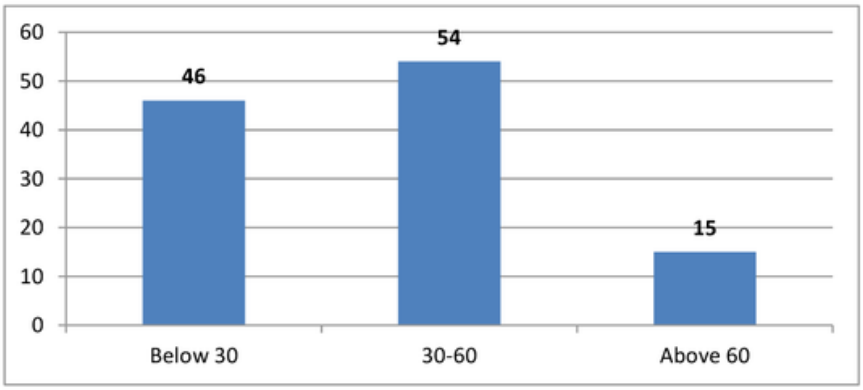
The data was further stratified into Pancytopenia, thrombocytopenia and anemia. The causes and frequencies in all the groups were calculated.

Pancytopenia was detected in 66 out of 115(57.3%) cases. Among them Megaloblastic anemia comprised of 29 (25.2%). Aplastic anemia was found in 10 (8.6%) of the cases

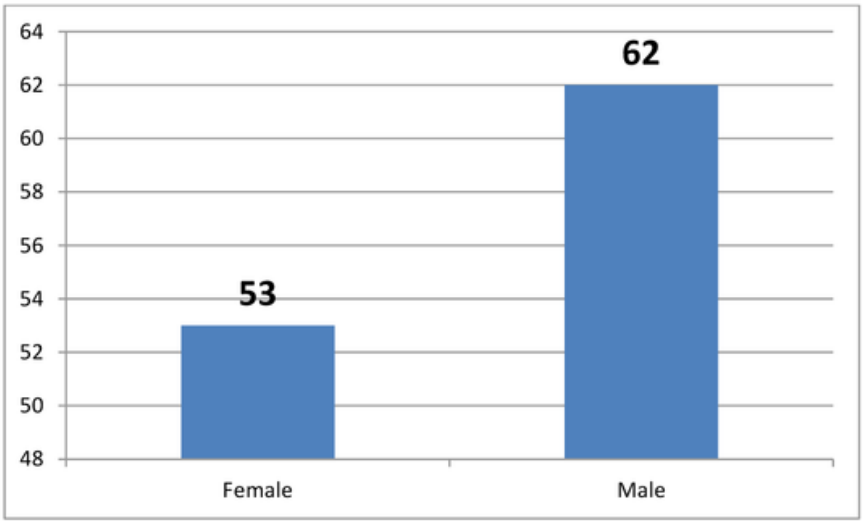
and a similar percentage 10 (8.6%) of patients had multiple myeloma. Disseminated intravascular coagulation was detected in 4 (3.4%). Drug induced myelo suppression was detected in 2 (1.7%) and another 2 (1.7 %) had myelodysplasia.

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%). Dengue hemorrhagic fever was diagnosed in 4(3.4 %) of them. 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:



Gender-wise distribution:



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	1	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 myelo suppression	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 tendency[10]. 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. 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 play[11]. 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 studies[12]. 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 thrombocytopenia[12] 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 of Megaloblastic anemia seem 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.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 adults[15]. 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[16]. Similarly, in the studies by *Khodke et al* [17] and *Tilak et al* [13]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[18]. Acute leukemia was the third common cause of Pancytopenia in the study of *Varma* and *Dash*[19]. Similarly, in the study of *Savage et al*[20] 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 being in accordance with our study. Acute Lymphoblastic Leukemia (ALL) was the commonest acute leukemia in the pediatric age while Acute Myeloid Leukemia 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 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. 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 malaria.

References:

1. Iqbal W, Hassan K, Ikram N, Nur S. Aetiological breakup of 208 cases pancytopenia. *J Rawal Med Coll* 2001;5(1):7-9.
2. Mussarat N, Raziq F. The incidence of underlying pathology in pancytopenia. An experience of 89 cases. *J Postgr Med Inst* 2004; 18(1).76-9.
3. Jan AZ, Zahid B, Ahmad S, Gul Z. Pancytopenia in children: A 6-year spectrum of patients admitted to Pediatric Department of Rehman Medical Institute, Peshawar. *Pak J Med Sci* 2013;29(5):1153-1157.
4. Qazi RA, Masood A. Diagnostic evaluation of pancytopenia. *J Rawal Med Coll* 2002;6(1):30-36.
5. Jha A, Sayami G, Adhikari RC, Panta AD, Jha R. Bone marrow examination in cases of pancytopenia.Wallace, Mark R., et al. "Endemic infectious diseases of Afghanistan." Clinical Infectious Diseases 34.Supplement 5 (2002): S171-S207.
6. B N Gayathri and Kadam Satyanarayan Rao Pancytopenia: A Clinico Hematological Study *J Lab Physicians*. 2011 Jan-Jun; 3(1): 15–20. doi: 10.4103/0974-2727.78555
7. Elizabeth P. Weinzierl MD,PhD, Daniel A. Arber MD The Differential Diagnosis and Bone Marrow Evaluation of New-Onset Pancytopenia *Am j clin path* DOI: http://dx.doi.org/10.1309/AJCP50AEEYGREWUZ 9-29 First published online: 1 January 2013
8. Tareen, S. M., Bajwa, M. A., Tariq, M. M., Babar, S., & Tareen, A. M. (2011). Pancytopenia in two national ethnic groups of Baluchistan. *J Ayub Med Coll Abbottabad,* 23(2), 82-6.

9. Weinzierl, Elizabeth P., and Daniel A. Arber. "The differential diagnosis and bone marrow evaluation of new-onset pancytopenia." *American journal of clinical pathology* 139.1 (2013): 9-29.
10. Modood-ul-Mannan, Anwar M, Saleem M, Wigar A, Ahmad MA. Study of serum vitamin B12 and folate levels in patients of megaloblastic anemia in northern Pakistan. *J Pak Med Assoc* 1995; 45: 187.
11. Durrani, Saadia Haroon, et al. "Incidentally diagnosed bicytopenia showing a wide spectrum of pathologies on bone marrow morphology." *KJMS* 8.2 (2015): 247.
12. Shiraz Jamal Khan, Yasir Abbass, and Mumtaz Ali Marwat, "Thrombocytopenia as an Indicator of Malaria in Adult Population," Malaria Research and Treatment, vol. 2012, Article ID 405981, 4 pages, 2012. doi:10.1155/2012/405981
13. Tilak V, Jain R. Pancytopenia - A clinico-hematologic Analysis of 77 cases. *Indian J Pathol Microbiol* 1999;42:399-404.
14. Bhatnagar SK, Chandra J, Narayan S, Sharma S, Singh V, Dutta AK. Pancytopenia in children: Etiological profi le. *J Trop Pediatr* 2005;51:236-9.
15. Jha A, Sayami G, Adhikari RC, Panta AD, Jha R. Bone marrow examination in cases of pancytopenia.
16. SP, Kumar Kumar R, Kalra H, Anand AC, Madan H. Pancytopenia - A six year Study. *JAPI* 2001;49:10781081.
17. Khodke K, Marwah S, Buxi G, Yadav RB, Chaturvedi NK. Bone Marrow Examination in Cases of Pancytopenia. *JIACM* 2001;2:55-59.
18. Bashwri LA. Bone marrow examination. Indications and diagnostic value. *Saudi Medi J*. 2002;23:191-6.

19. Varma N, Dash S. A reappraisal of underlying pathology in adult patients presenting with pancytopenia. *Trop Geogr Med* 1992;44:322-7.
20. Savage DG, Allen RH, Gangaidzo IT et al. Pancytopenia in Zibabwe. *Am J Med Sci* 1999;317:22-32.

ETIOLOGY AND FREQUENCY OF VARIOUS CYTOPENIAS PRESENTING IN MEDICAL UNIT ON THE BASIS OF PERIPHERAL SMEAR AND BONE MARROW EXAMINATION

ORIGINALITY REPORT

11%	9%	8%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	ispub.com Internet Source	2%
2	www.ncbi.nlm.nih.gov Internet Source	1%
3	doi.org:8080 Internet Source	1%
4	www.jmedsci.com Internet Source	1%
5	www.nepjol.info Internet Source	1%
6	Parajuli, S, and A Tuladhar. "Correlation of bone marrow aspiration and biopsy findings in diagnosing hematological disorders - a study of 89 cases", Journal of Pathology of Nepal, 2014. Publication	1%
7	Vaidya, S. "Evaluation of bone marrow in cases of pancytopenia in a tertiary care hospital",	1%

	Journal of Pathology of Nepal, 2015. Publication	
8	Pathak, R, A Jha, and G Sayami. "Evaluation of bone marrow in patients with pancytopenia", Journal of Pathology of Nepal, 2012. Publication	1%
9	www.gjms.com.pk Internet Source	1%
10	healthrenaissance.org.np Internet Source	<1%
11	Bar, I., D. Stav, G. Fink, A. Peer, T. Lazarovitch, and M. Papiashvilli. "Thoracic Empyema in High-Risk Patients: Conservative Management or Surgery?", Asian Cardiovascular and Thoracic Annals, 2010. Publication	<1%
12	icp-api.org Internet Source	<1%
13	www.kma.org.kw Internet Source	<1%
14	www.biomedscidirect.com Internet Source	<1%
15	Erlacher, Miriam, and Brigitte Strahm. "Missing Cells: Pathophysiology, Diagnosis, and Management of (Pan)Cytopenia in Childhood",	<1%

Frontiers in Pediatrics, 2015.
Publication

16 www.mjpch.com
Internet Source
<1%

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON
EXCLUDE MATCHES OFF