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PANCYTOPENIA;

STUDY FOR CLINICAL FEATURES AND ETIOLOGICAL PATTERN AT TERTIARY CARE SETTINGS IN ABBOTTABAD

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ABSTRACT... Background: Pancytopenia is an important hematological problem encountered in our day-to-day clinical practice. The aim of our study was to evaluate clinical features and etiological pattern of pancytopenia at tertiary care settings in Abbottabad. **Methods:** This prospective study was conducted at Northern Institue of Medical Sciences (NIMS) and Ayub Teaching Hospital Abbottabad from 25th August 2009 to 31st July 2010. A total of 85 patients fulfilling the criteria of pancytopenia were randomly selected by time-based sampling. Pancytopenia was diagnosed by anemia (hemoglobin ≤ 10.0g/dl), leucopenia (WBC ≤ 4.0×10^9/L) and thrombocytopenia (platelets ≤ 150×10^9/L). All data has been entered and analyzed by SPSS version 10.0. **Results:** Out of 85 patients, 62(72.94%) were males and 23(27.05%) females with M to F ratio of 2.69:1. The mean age (±SD) of males was 30.20±15.42 years, while that of females 35.12±16.31 years (p=0.20). Among clinical features, anemia and generalized weakness were the commonest (97.64%), followed by shortness of breath (88.23%). Majority 54(63.52%) had non-malignant disorders responsible for pancytopenia. Overall, the most common cause of pancytopenia was aplastic anemia noted in 30(35.29%) cases, followed by megaloblastic anemia 15(17.64%) and hypersplenism in 13(15.29%). **Conclusions:** On conclusion, aplastic anemia was the most common cause of pancytopenia in our study predominantly affecting young adult males. It was mainly due to use of toxic and ban-drugs by quacks and general practitioners at their clinics.

Key words: Pancytopenia, aplastic anemia, general practitioners, quacks, bone marrow examination.

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INTRODUCTION

Pancytopenia is an important hematological problem encountered in our day-to-day clinical practice. It is a decrease in all three cellular elements of peripheral blood leading to anemia, leucopenia and thrombocytopenia[1]. Pancytopenia usually presents with symptoms of bone marrow failure such as pallor, dyspnea, bleeding, bruising and increased tendency to infections[2]. The laboratory diagnosis of pancytopenia is evident by low values of hemoglobin (≤10.0 g/dl), white blood cells (≤4.0×10^9/L) and platelet counts (≤150×10^9/L). The incidence of various disorders causing pancytopenia varies according to geographical distribution and genetic mutations . It can result either from failure of production of hematopoietic progenitors in bone marrow, or malignant cell infiltration, or antibody-mediated bone marrow suppression, or ineffective hematopoiesis and dysplasia, and peripheral sequestration of blood cells in overactive reticulo-endothelial system[3]. The main causes of pancytopenia are aplastic anemia, hyper-splenism, myelodyplastic syndrome[4], nutritional deficiencies leading to megaloblastic anemia[5], sub-leukemic (acute) leukemias, multiple myeloma, paroxysmal nocturnal hemoglobinuria and infections such as HIV, miliary tuberculosis, brucellosis, and leishmaniasis.

A detailed history, physical examination and complete blood counts with reticulocyte count and peripheral blood smear remain essential for diagnosis. Profound neutropenia and

thrombocytopenia associated with sepsis and bleeding, most often reflect underlying marrow aplasia or leukemia, while glossitis, diarrhea and paresthesias are associated with megaloblastic anemia. Blast cells are seen on blood film of most patients having acute leukemias, whereas hypo-granulated and segmented neutrophils often indicate myelodyplastic syndrome. In addition, hyper-segmentation of neutrophils in pancyto-penic patients or abnormalities of erythrocyte morphology with low serum vitamin B_{12} and folate levels confirm megaloblastic anemia. Bone marrow examination is essential to determine the cause of pancytopenia, as it plays a major role in hematological malignancies, unexplained cytopenias and storage disorders[3]. Trephine biopsy is mainly undertaken when hypoplasia or aplasia of bone marrow being suspected on aspiration[6].

This study is important in Abbottabad context as majority of our patients visit quacks and general practitioners for their problems, who injudiciously prescribe toxic and ban-drugs from clinics (like chloramphenicol, cotrimoxazole, phenylbuta-zone, metamizole etc) due to low costs. In-addition, due to poverty peoples could not take meat, fruits and green leafy vegetables, which are the main sources of vitamin B_{12} and folate. Furthermore, this study provides a new forum for approaching the patients with pancytopenia. There are only few studies in Pakistani literature on clinical spectrum of pancytopenia. The present study was undertaken to evaluate clinical features and etiological pattern of pancytopenia at tertiary care settings in Abbottabad.

PATIENTS AND METHODS

This prospective, descriptive, hospital-based study has been conducted at Northern Institute of Medical Sciences (NIMS) and Ayub Teaching Hospital Abbottabad from 25th August 2009 to 31st July 2010. The local Ethical Committees of the Institutes approved the study protocol and all patients gave written and informed consent. A total 85 patients of either sex having pancytopenia, from indoor and outdoor medical departments of above mentioned hospitals, were studied. Those who were less than 13 years, pregnant females, previously diagnosed cases, received blood transfusions recently and on cytotoxic drug therapy, excluded from this study. Pancytopenia has been diagnosed by the presence of anemia (hemoglobin $\leq$ 10.0g/dl), leucopenia (WBC $\leq$ 4.0×10^9/L) and thrombocytopenia (platelets $\leq$ 150×10^9/L). All patients fulfilling the criteria of pancytopenia were randomly selected for this study by using technique of time-based sampling.

A pre-designed proforma was developed to record history, examination details and investigation reports. All patients were thoroughly evaluated with special emphasis on history of prior drugs intake, exposure to chemical agents and radiation either by occupational, accidental or by medical treatment. History of recent viral infections, fever, weight loss, bleeding (e.g. gums, nose, mouth, vagina) were noted. Dietary history with special focus on animal products (e.g. meat, milk, eggs), any episodes of abdominal pain, diarrhea/ bulky stools. Also any history of worm expulsion in stool and blood transfusions were noted. All patients have undergone for general and systemic examinations to note anemia, jaundice, pedal edema, mouth ulcers, bone pain, splengomegaly, hepatomegaly and lymphadenopathy. The laboratory analyses include complete blood count (CBC) with absolute values and reticulocyte counts which were conducted on an automated blood analyzer (Sysmex). Peripheral blood smear was examined manually after being stained with giemsa's stain and looked for malarial parasite (MP). Differential leukocyte count and red cell morphology were also measured manually. Hepatitis A serology, chest radiograph and abdominal ultrasound examinations have been performed in selected cases. All patients have undergone for bone marrow aspiration and wherever required, a trephine biopsy was also taken.

All data has been entered and analyzed by SPSS version 10.0. The age was described as mean ($\pm$SD), while discrete variables like gender, clinical features and causes of pancytopenia were presented in percentages.

RESULTS

Eighty five patients were enrolled during eleven months of study for analysis of clinical features and various causes of pancytopenia in relation to age and gender. There were 62(72.94%) males and 23(27.05%) females, with M to F ratio 2.69:1. The age of our patients ranged from 13-70 years. The mean age of males was 30.20±15.42 years (mean ±SD), while of females 35.12±16.31 years. This has been shown in table-I. Among clinical features, anemia and generalized weakness were the commonest (97.64%) for each, followed by shortness of breath (88.23%), mass in abdomen (55.29%), fever (52.94%), bleeding manifestations such as epistaxis, hematemesis and malena (50.58%), abdominal pain (50.58%), bone pain (44.70%). The least common features were ascites (5.88%) and jaundice (8.23%), followed by pedal edema (11.76%). The details of various clinical features of pancytopenics were listed in table-II.

In our study, majority 54(63.52%) had non-malignant disorders responsible for pancytopenia. Out of 85 patients, the most common cause of pancytopenia was aplastic anemia noted in 30(35.29%) cases, followed by megaloblastic anemia 15(17.64%) and hypersplenism in 13(15.29%). Acute leukemias were observed in 11(12.94%), myelodysplastic syndrome in 06 (7.05%) and chronic malaria in 05(5.88%) patients. Other less common causes of pancytopenia were multiple myeloma 02(2.35%), non-Hodgkin's lymphoma 02(2.35%) and no cause found in 01(1.17%) patient. All of these disorders were more common in males than females. The etiologies of pancytopenic patients were shown in table-III.

Out of 30(35.29%) cases of aplastic anemia, 23(76.66%) were males and 07(23.33%) females with M to F ratio 3.28:1. Mean age of males was 23.4 years, while that of females 41.3 years. Majority 20(66.66%) patients of aplastic anemia had history of taking drugs from quacks or general practitioners. The exact nature of drugs were not known to patients. The remaining 10(33.33%) patients of aplastic anemia were caused by viral infections and exposure to chemicals. Out of 15(17.64%) patients of megaloblastic anemia, 12(80%) had vitamin B_{12} deficiency and 3(20%) were folate deficient. There were 12(80%) males and 3(20%) females with M to F ratio 4:1. Mean age of males was 34.21 years, while that of females 42.1 years. Amongst the patients with B_{12} deficiency, 10(83.33%) had history of nutritional deficiency (i.e. lack of animal products in diet), 01(8.33%) had history of ileal resection due to sub-acute intestinal obstruction caused by intestinal tuberculosis and 01(8.33%) had malabsorption

Males	62(72.94%)	30.20±15.42
Females	23(27.05%)	35.12±16.31
Total	85	34.73±17.73
p-value	---	p=0.20 (non-significant)

Table-I. Age and sex distribution in pancytopenic patients (n=85)

Clinical Features	No. of patients	%age
Anemia	83	97.64
Generalized weakness	83	97.64
Shortness of breath	75	88.23
Mass in abdomen	47	55.29
Fever	45	52.94
Bleeding	43	50.58
Abdominal pain	43	50.58
Bone pain	38	44.70
Purpuric spots	31	36.47
Mouth ulcers	23	27.05
Lymphadenopathy	11	12.94
Pedal edema	10	11.76
Jaundice	7	8.23
Ascites	5	5.88

Table-II. Showing different clinical features of pancytopenic cases.

Diseases	No. of patients	%age
Aplastic anemia	30	35.29
Megaloblastic anemia	15	17.64
Hypersplenisin	13	15.29
Acute Leukemias	11	12.94
Myeloclysplastic Syndrome	06	7.05
Chronic malaria	05	5.88
Multiple myeloma	02	2.35
Non-Hodgkin's Lymphoma	02	2.35
None	01	1.17

Table-III. Showing etiologies of pancytopenia (n=85)

features on history. Similarly, amongst patients with folate deficiency, 02(66.66%) had nutritional deficiency and 01 (33.33%) had mal-absorption cause.

Hypersplenism was diagnosed in 13(15.29%) patients and majority 10(76.92%) had decompensated liver cirrhosis, 02(15.38%) had tropical splenomegaly syndrome and 01(7.69%) had no known cause. There were 7(53.84%) males and 06(46.15%) females with M to F ratio of 1.16:1. Mean age of males was 49.3 years, while that of females 42.7 years. Out of 10(76.92%) patients of liver cirrhosis, 06(60%) had anti-HCV reactive, 03(30%) had HBsAg reactive and 01(10%) had Wilson's disease. Acute leukemias were observed in 11(12.94%) patients and comprised of 08(72.72%) cases of acute myelogenous leukemia, 02(18.18%) cases of acute lymphoblastic leukemia and 01(9.09%) patient of chronic myeloid leukemia. There were 07(63.63%) males and 04(36.36%) females with M to F ratio of 1.75:1. Mean age of males was 44.7 years, while that of females 52.3 years.

DISCUSSION

Pancytopenia is a serious hematological problem encountered in clinical practice which predisposes to anemic manifestations, infections, and bleeding tendencies. Underlying it. there are multiple causes which can be diagnosed by bone marrow aspiration and trephine biopsy[7].

Our study clearly demonstrated more risk for pancytopenia in younger peoples with age ranging from 13-47 years. Also prevalence rate among males were 72.94% and that of females 27.05% with M to F ratio of 2.69:1. This is quite similar to study conducted in Larkana by Jalbani A[8], who also showed 72.5%% males and 27.5% females with M to F ratio 2.6:1. On the contrary, another study in Karachi by Aziz T[9] showed majority (59%) of their pancytopenic patients were females and 41(%) males. This may be related to geographical variation for incidence of pancytopenia. In Northern areas, males are the main source of earning for their family and they usually spent much of their time outdoor by working in fields and industries, hence more exposed to agricultural insecticides and pesticides, or industrial toxins, or radiation. On the contrary, females usually remain indoor in household activities, hence less exposed to these hazards and they are mostly reluctant for early medical advice due to illiteracy. On the other hand, there is urban lifestyle in Karachi, where females also perform jobs almost in every sector along males hence are equally exposed to chemicals and environmental toxins.

In present study, anemia, generalized weakness and shortness of breath were the most common clinical features in pancytopenic patients comprising of (97.64%), (97.64%) and (88.23%) respectively. Similar results have been reported in studies by Aziz T[9], Ishtiaq O[10] and Niazi M[11]. The frequencies of other clinical features were variable and different from these studies probably due to broad spectrum of etiologies behind pancytopenia.

Aplastic anemia was the most common cause of pancytopenia in our patients accounting for 35.29%. Majority were young adult males with mean age of 23.4 years. This is consistent with study by Tariq M[12], Niazi M[11], Jalbani A[8] and Aziz T[9], whom showed frequencies of aplastic anemia in

36%, 38.3%, 32.5% and 31.88% patients respectively. Epidemiologically, aplastic anemia has a pattern of geographic variation opposite to that of leukemia, as it is more common in developing countries than in western world. Large prospective studies indicate an annual incidence of two new cases per million populations in Europe and Israel. The increased incidence of aplastic anemia in Orient may probably be related to environmental factors such as increased exposure to toxic chemicals rather than genetic involvement, as this increase has not been observed in peoples of Oriental ancestry presently living in United States[13,14]. In addition, easy availability of over the counter medications in developing countries may be implicated in higher percentage of aplastic anemia patients, as studies from Thailand have demonstrated pesticide exposure as a common etiological agent for aplastic anemia[15,16]. In our study, out of 30(35.29%) patients of aplastic anemia, majority 20(66.66%) had history of taking drugs from quacks or general practitioners before symptoms of pancytopenia. Other factors responsible for aplastic anemia were viral infections, exposure to chemicals and radiation in industries, overzealous exposure to hydrocarbons from motor vehicles and use of insecticides and pesticides by farmers in their fields. Similar results have been reported in a study by Jalbani A[8]. Megaloblastic anemia was the second most common cause of pancytopenia in our patients (17.64%). Its frequency ranges from as low as 13.04% in a study by Memon S[17] to as higher as 40.9% by Aziz T[9]. The results of our study were quite closer to study by Tariq M[12], who found megaloblastic anemia in 16% of their cases. Megaloblastic anemia, due to vitamin B_{12} and folate deficiencies, is now a well-recognized and established cause of pancytopenia and there is increased health concern about its consequences worldwide[18]. Although we were unable to determine exact cause of megaloblastic anemia, but vitamin B_{12} deficiency is more common in adults, while folate deficiency in children. In addition, poor nutrition may be responsible for increased frequency of megaloblastic anemia (vitamin B_{12} deficiency is more prevalent than folate deficiency) in Northern areas of Pakistan[19]. However, folate deficiency could be caused by chronic diarrheas and malabsorptive states apart from poor nutrition. As we discovered vitamin B_{12} deficiency (nutritional) in majority of our patients (80%), which is comparable with results of studies by Tariq M[12], Jalbani A[8], Aziz T[9] and Mannan M[19].

In present study, hypersplenism was preset in 15.29% patients and majority has decompensated cirrhosis of liver leading to portal hypertension. This is quite closer to study by Iqbal W[3], who found hypersplenism in 14.4% of their cases. However, Jalbani A[8] and Ishtiaq O[10] have found hypersplenism in 22.5% and 19% of patients respectively and majority had decompensated liver cirrhosis similar to our study. Acute leukemias were noted in 12.94% of our patients. This is consistent with study by Tariq M[12], who discovered acute leukemias in 14% of their patients. In this study, acute myelogenous leukemia was dominant malignant disorder comprising of 72.72%. This is in contrast to study by Tariq M[12], who found acute lymphoblastic leukemia as commonest disorder in 85% of their patients. The incidence of acute lymphoblastic leukemia is lower in our country as compared to United States, where approximately 2500 cases per annum are diagnosed.

CONCLUSIONS

From this study, we concluded that aplastic anemia was the commonest cause for pancytopenia, followed by megaloblastic anemia and hypersplenism. Aplastic anemia predominantly affects young adult males and main cause was use of toxic and ban-drugs by quacks and general practitioners at their clinics. Furthermore, bone marrow aspiration and trephine biopsy were useful diagnostic tools in evaluating the etiology of pancytopenia.

RECOMMENDATIONS

Quacks must be banned at any cost and general practitioners strictly warned regarding the use of toxic and ban-drugs at their clinics. Preventive measures should be adopted by those working in fields, chemical industries and radiation departments. Public awareness regarding the use

of balanced diet should be highlighted via electronic media. In addition, proper cooking guidelines for foods should be given in order to maintain its nutritious value. Furthermore, large-scale studies needed to determine exact causes and incidence of pancytopenia.

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REFERENCES

1. Kar M, Ghosh A. **Pancytopenia.** J Indian Acad Clin Med 2002;3(1):29-34.
2. Khan NM, Ayub M, Nawaz KH, Naqi M, Hussain T,Shujaat H. **Pancytopenia:Clinicopathological Study Of 30 Cases at Military Hospital, Rawalpindi.** Pak J Pathol 2001;12(2):37-41.
3. Iqbal W, Hassan K, Ikram N, Nur S. **Aetiological Breakup in 208 Cases of Pancytopenia.** J Rawal Med Coll 2001;5(1):7-10.
4. Ishtiaq O, Baqai ZH, Anwer F, Hussain N. **Patterns of Pancytopenia Patients in a General Medical Ward and a Proposed Diagnostic Approach.** J Ayub Med Coll Abbottabad Janu-Mar 2004;16(1):8-13.
5. Khalid G, Moosani AM, Ahmed L. **Megaloblastic anemia seen in 48 cases of Pancytopenia.** Ann Abbasi Shaheed Hosp Karachi Med Dent Coll Dec 2005;10(2):742-744.
6. Rahim F, Ahmad I, Islam S, Hussain M, Khattak TAK, Bano Q. **Spectrum of hematological disorders in children observed in 424 consecutive bone marrow aspirations/biopsies.** Pak J Med Sci 2005;21:433-6.
7. Dodhy MA, Bokhari N, Hayat A. **Etiology of Pancytopenia ; a five-year experience.** Ann Pak Inst Med Sci Apr-Jun 2005;1(2):92-95.
8. Jalbani A, Ansari IA, Shah AH, Gurbakhshani KM, Chutto M, Solangi GA. **Pancytopenia: Study of 40 patients at CMC hospital, Larkana.** Professional Med J Mar 2010;17(1):105-110.
9. Aziz T, Ali L, Ansari T, Liaquat HB, Shah S, Ara J. **Pancytopenia: Megaloblastic anemia is still the commonest cause.** Pak J Med Sci Janu-Mar 2010;26(1):132-136.
10. Ishtiaq O, Baqai HZ, Anwer F, Hussain N. **Patterns of Pancytopenia patients in a General Medical Ward and a proposed diagnostic approach.** J Ayub Med Coll Abottabad 2004;16(1):8-13.
11. Niazi M, Raziq F. **The incidence of underlying pathology in Pancytopenia - an experience of 89 cases.** J Postgrad Med Inst Jan-Mar 2004;18(1):76-79.
12. Tariq M, Khan N, Basri R, Amin S. **Etiology of Pancytopenia.** Professional Med J Jun 2010;17(2):252-256.
13. Bakhshi S. **Aplastic Anemia- Facts and statistics.** E Medicine J 2001;2(6):1.
14. Young NS. **Acquired Aplastic Anemia.** Ann of Int Med 2002;136(7):534.
15. Issaragrisil S, Chansung K, Kaufman DW, Sirijirachai J, Thamprasit T, Young NS. **Aplastic anemia in rural Thailand: its association with grain farming and pesticide exposure.** Am J Public Health 1997;87:1551.
16. Kaufman DW, Issaragrisil S, Anderson T, Chansung K, Thamprasit T, Sirijirachai J. **Use of household pesticides and the risk of aplastic anemia in Thailand.** Int J Epidemiol 1997;26:643-50.
17. Memon S, Shaikh S, Nizamani AA. **Etiological spectrum of pancytopenia based on bone marrow examination in children.** J Coll Physicians Surg Pak 2008;18(3):163-7.
18. García-Casal MN, Osorio C, Landaeta M, Leets I, Matus P, Fazzino F. **High prevalence of folic acid and vitamin B_{12} deficiencies in infants, children, adolescents and pregnant women in Venezuela.** Eur J Clin Nutr 2005;59(9):1064-70.
19. Mannan M, Anwar M, Saleem M, Wigar A, Ahmad MA. **Study of serum vitamin B_{12} and folate levels in patients of megaloblastic anemia in Northern Pakistan.** J Pak Med Assoc 1995;45:187.