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RESEARCH ARTICLE

EVALUATION OF PANCYTOPENIA BY BONE MARROW EXAMINATION: EXPERIENCE IN A TERTIARY HOSPITAL

[1]Dr. Adil H. Siddiqie, [*,2]Dr. Bilal Musharaf Banday and [3]Dr. Afaq Khan

[1]lecturer, Department of Pathology Government Medical College, Srinagar, Jammu and Kashmir, India
[2] Senior Demonstrator, Department of Pathology Government Medical College, Srinagar, Jammu and Kashmir, India
[3]Consultant JLNM hospital Srinagar, Jammu and Kashmir, India

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Abbreviations:
BMA Bone Marrow Examination,
HSM *Hepatosplenomegaly,*
PRCA Pure Red Cell *Aplasia*,
AA *Aplastic Anaemia*
Conflict of Interest : None

ABSTRACT

Background: Pancytopenia is a common problem encountered in routine hospital practice .It can be a manifestation of relatively trivial treatable cause to serious malignant disorders both haematological as well as non haematological .Bone marrow examination provides a definitive diagnosis for the further management of these patients .
Objectives: To study the various patterns of presentation of pancytopenia and use of bone marrow examination as a diagnostic tool.
Materials and Methods: It was a prospective study with 108 pancytopenia patients subjected to bone marrow aspiration and biopsy, wherever required in the Department of Pathology Government Medical College Srinagar and its associated hospitals.
Results: In 108 patients of pancytopenia subjected to bone marrow examination ,the commonest cause was found to be Megaloblastic Anaemia (52.7%), followed by haematological malignancies (24.07%) Infections accounted for 12.9%of patients Metastasis was seen in 3.7% cases. Aplastic anaemia and PRCA were seen in 1.8% patients each.
Conclusion: The causation of pancytopenia is extremely varied and multifactorial. Numerous studies including peripheral smear examination, bone marrow examination can help to arrive at a correct diagnosis which can be confounding at times.

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INTRODUCTION

Pancytopenia is an important clinico-haematological entity that is encountered in day to day clinical practice. The causes of peripheral pancytopenia may be new onset pancytopenia with a short history or may have a longer duration. The causes are multifactorial ranging from infective causes, haematological malignancy, metastasis, and peripheral destruction of cells. As more patients are on cytotoxic therapy, pancytopenia is seen more often than before. The presenting symptoms of pancytopenia are due to anaemia, neutropenia and thrombocytopenia. Wherever, in absence of any overt sign of haematological malignancy, many clinicians prefer to postpone bone marrow aspirations for few days. Nutritional Megaloblastic anaemia is a leading cause of pancytopenia in developing countries in contrast to developed countries. Infective causes are also more common causes of pancytopenia here (Elizabeth, 2013). Bone marrow aspiration and biopsy is a safe and effective procedure with minimal risk and provides a diagnosis in most of the cases. Although it is an invasive procedure, there have not been many reported complications. As more preference is given to posterior iliac and anterior tibial aspirations nowadays instead of sternum for safety, complications have been very minimal with an odd case of hematoma formation reported. Even in presence of severe thrombocytopenia, we performed aspirations with no complications. Patient compliance is also excellent inspite of initial anxiety.

MATERIALS AND METHODS

A prospective study was carried out in the Department of Pathology of Govt. Medical College Srinagar from 01 May 2013 to 31 December 2015. A total of 418 bone marrow aspirations were done during this period. Among these total of

Corresponding author: Dr. Bilal Musharaf Banday,
Department of Pathology Government Medical College, Srinagar, J&K, India.

108 cases of pancytopenia cases were referred for BMA during the period. Detailed history along with physical examination was done. The following criteria were adopted for labelling patient as pancytopenia:

1. Haemoglobin level below 13.5gm/dl for males and below 12gm/dl for females.
2. Total Leukocyte count below 4 x 10^9/L.
3. Platelet count below 150 x 10^9/L.

A complete history which included age, sex, history of any medication, exposure to pesticides, drugs, radiation, infections etc was taken. Physical examination was done with evaluation of jaundice, pallor, HSM, lymphadenopathy. Blood counts were done using Siemens Adiva 5 part haematology analyser. Manual cross checking was done by making peripheral blood smears stained with Leshmians stain. Bone marrow aspiration was done in all cases of pancytopenia, where the cause was not obvious. Bone marrow biopsy was done in cases with HSM, dry tap and wherever malignancy was suspected. Bone marrow slides were stained by Giemsa stain and Leshmians stain.Iron staining was done by Prussian blue method. Auxiliary investigations including LFT, KFT, serological investigations for infectious diseases like enteric fever, brucellosis, and hepatitis.HIV was done.

RESULTS

A total of 410 bone marrow aspirations were performed during the period. Out of these 108 patients presented with pancytopenia. Bone marrow aspiration was done in all of the cases with biopsy wherever required .Diagnosis was done in all the cases supplemented with clinical history and special stains including reticulin and PAS. There were 48 males and 60 females with a male female ratio of 0.8:1. The mean age was 49 years with a range of 14-90 years.

Table 1. Bone Marrow findings in cases of Pancytopenia

S.no	Disease	No of cases (n=108)	%age
1	Megaloblastic Anaemia	57	52.7
2	Hematological Malignancy	26	24.07
3	Infections	14	12.9
4	Metastasis	4	3.70
5	Aplastic Anaemia	2	1.8
6	PRCA	2	1.8
7	Myelofibrosis	1	0.9
8	Hypersplenism	1	0.9
9	Hemopagocytosis	1	0.9
	TOTAL	108	100%

The commonest finding was Megaloblastic Anaemia seen in 52.7% as shown in table 1. Males comprises 24 cases and females 33 cases with a male female ratio of 0.92:1 The age ranged from 17years to 90years with mean age of 43years.The difference in frequency of various causes of pancytopenia is due to the differences due to geographical differences, nutritional status, exposure to pesticides and infections. In a study by Savage et al and Khunger et al the most common cause of pancytopenia was megaloblastic anaemia followed by hypoplastic anaemia. Haematological malignancies constituted 26 cases (24.07%) as shown in Table 2. Acute Leukaemia comprised 50% of haematological malignancies with 9 cases of Acute Myeloid Leukaemia along with 4 patients were diagnosed with ALL. The most common malignancy manifesting as pancytopenia was Acute Myeloid Leukaemia. Plasma cell myeloma, MDS and NHL were the other three haematological malignancies. Although number of plasma cell myeloma amongst haematological malignancy was overall more in all the aspirations performed. However, only two cases presented as pancytopenia.

Table 2. Haematological Malignancies presenting with pancytopenia

Haematological Malignancy	No of Cases (n=26)	% age
AML	9	34.61%
ALL	4	15.38
MDS	7	26.92
NHL	4	15.38
Plasma cell Myeloma	2	7.69
TOTAL	26	100%

Two cases of aplastic anaemia were seen in the study. One was a 35 year pregnant female while other patient was an18 year's young male. Two patients with pure red cell aplasia were seen in the study, both females with ages of 38 and 68 years.

DISCUSSION

The normal adult marrow produces about $1.7x10^{11}$ RBCs, $1x10^{11}$neutrophils and $2x10^{11}$ platelets each day and thus it has a tremendous capacity to substantially increase the output of these cells when necessary with the help of growth factors and cytokines (Madhuchanda, 2002). A pluripotent stem cell can begin to differentiate leading to individual clone of differentiated cells .The circumstances that lead to pancytopenia due to bone marrow failure include both defect in the stem cells or micro-environment. However, the former reasons predominate (Young NS, 1995).

Thus different mechanisms leading to pancytopenia appear to be:-

1 Decrease in Hematopoietic cell production as a result of replacement by abnormal /malignant cells, Folate or B12 deficiency.
2 Sequestration of hematopoietic cells as in hypersplenism.
3 Increased destruction, immune mediated or drug induced.

Megaloblastic anaemia was the commonest cause for pancytopenia in our study. The exact cause of megaloblastic anaemia could not be ascertained in all the cases. However nutritional cause was attributed to two females and one male who were suffering from tropical sprue. Two young males and one female were found to be having drug induced megaloblastic anaemia subsequently leading to pancytopenia. Although serum folic acid and vitamin B 12 were not assessed as a part of study profile but levels were done in the hospital during work up of the patients. A significant number; 24.07% of patients were diagnosed with haematological malignancy Acute leukaemia was seen in 13 patients –50% of the overall haematological malignancy patients. Acute Myeloid leukaemia

was found in 9 patients and ALL was seen in 4 patients. Pancytopenia as a presenting symptom is seen in 8-12-% of patients (Shruti R, 2015). Pancytopenia from bone marrow failure is also an important feature of acute leukaemia, the latter stages of chronic leukaemia, MPD and MDS. The mechanism is multifactorial including suppression of normal haematopoiesis as well as bone marrow infiltration by abnormal clone of cells. NHL and chronic leukaemia can also lead to pancytopenia when there is significant bone marrow infiltration. Amongst chronic leukaemia, hairy cell leukaemia most often presents with pancytopenia (Frosololdati, 1994). However, we found no such case, although 4 cases of NHL presented with pancytopenia. Pancytopenia in multiple myeloma is unusual and is attributed to reasons most often due to abnormal clone of plasma cells replacing normal hematopoietic elements. Antecedent causes include fas-ligand mediated apoptosis or cytokine mediated bone marrow failure. Renal failure induced erythropoietin deficiency can lead to a hypoplastic marrow (Hungambali, 2015). MDS seen in 26.92 % of our study amongst haematological malignancy is characterised by progressive bone marrow failure with several subsets progressing to AML. The higher grade subtypes that demonstrate extensive bone marrow failure such as refractory anaemia with multilineage dysplasia more commonly present with pancytopenia (Barrettj, 2000). Infections lead to pancytopenia has varied causes including enteric fever (4cases), tuberculosis (1case) especially miliary tuberculosis (Mert, 2001). Although leucopenia with neutropenia is more common in overwhelming infections, pancytopenia can also be a presenting feature. It has been attributed to bone marrow suppression, necrosis, infection associated hemophagocytosis syndrome, DIC and development of septicaemia (Osama I, 2004; Tilak, 1999). Metastasis seen in 3.70 % of patients more often presents as anaemia with bicytopenia and leukoerythroblastc picture on peripheral blood film but occupation of marrow spaces as direct replacement and fibrosis can lead to pancytopenia (Makoni, 2004; Brochamer Jr, 1977; Krishnan, 2007).

Hypersplenism seen in one case presented with huge splenomegaly with peripheral cytopenia. The patient was a young male with a recent history of malaria. Hypersplenism has a wide range of causes, in which peripheral cytopenias are a dominant finding. The mechanism is thought to be a combination of haemolysis, sequestration and premature destruction of red cells. A large percentage upto 90% of platelets, 30% of red cell mass and 65% of granulocytes can be sequestrated in a massively enlarged spleen (Rosen field, 1991; Kumar, 2012). Amongst two cases of aplastic anaemia one was pregnant female. AA during pregnancy is not unknown. In fact AA was first described in a pregnant woman (Van Besien, 1991). It has been seen that pancytopenia improves after abortion or delivery Chronic PRCA usually present as anaemia but can also present as pancytopenia which it did it our study. Diseases that cause fibrosis of bone marrow also lead to pancytopenia and include primary myeloid neoplasms, malignant lymphomas, metastatic carcinomas, inflammatory reactions granulomatous reaction and osteopathies. Primary myelofibrosis most often presents with bone marrow fibrosis and cytopenias.

Conclusion

Pancytopenia has a wide spectrum of aetiologies ranging from infectious causes to malignancies, both primary haematological as well as metastatic. Bone marrow aspiration provides the diagnosis and is an indispensible tool in the management of these patients

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