Bone marrow examination findings in cases of pancytopenia- a study from central India

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Abstract

Background and Objectives: Pancytopenia is one of the most common indications for bone marrow (BM) examination. There are spectrums of condition involving the bone marrow (BM) that can present with pancytopenia and include malignant as well as benign diseases. The objective of this study is to evaluate the BM findings in cases of pancytopenia.

Materials and Methods: This was a retrospective study of 156 cases of pancytopenia presenting over a period of 3 years. Data were retrieved from laboratory and clinical records and were analysed.

Results: Out of 156 cases, the most common cause for pancytopenia in this study was megaloblastic anemia (25.6%), followed by acute leukemia (16%), hypoplastic marrow (14%), metastatic solid tumors (8.9%), myelodysplastic syndrome (MDS) (7.1%), lymphomas (5.7%), plasma cell dyscrasia(3.8%). Along with these there were many benign yet rare causes which may present with pancytopenia like Hemophagocytic syndrome (1.2%), Histoplasmosis (0.6%), Leishmaniasis (0.6%) and Gaucher's disease (0.6%). Bone marrow examination (combining both aspirate and biopsy) alone was sufficient in diagnosing 55% of cases, while remaining cases require additional details like clinical findings (for cases of MDS, viral infection, hypersplenism, autoimmune, septicemia) and special investigations like hemoglobin electrophoresis for hemoglobinopathy. In only 3.8% cases, BME was inconclusive.

Conclusion: BME is an important investigation in diagnostic work up of cases of pancytopenia. In majority of cases, it can provide an accurate diagnosis or at least can guide the approach towards diagnosis and management. Thus, it should be performed in all cases of persistent pancytopenia and should be evaluated in light of clinical details and supportive investigations.

Keywords: Pancytopenia, Bone marrow aspiration biopsy, Causes, Clinical presentation

Access this article online	
Quick Response Code:	Website: www.innovativepublication.com
	DOI: 10.5958/2394-6792.2016.00089.2

Introduction

Pancytopenia is an important clinical entity which is defined as reduction in the number of all the three series (WBC's, RBC's and platelets) in peripheral blood[1].

Pancytopenia is a clinical outcome of many diseases that involve bone marrow either primarily or secondarily. Management of pancytopenia cases depends on the severity of pancytopenia and treatment of the underlying pathology[2].

There are various mechanisms for development of pancytopenia and this include reduced or ineffective hematopoiesis and increased destruction by either sequestration or destruction by antibodies[3].

In cases of pancytopenias, patient usually presents with clinical features attributable to decreased number of RBC's, platelets or WBC's i.e., pallor, easy fatiguability, bleeding, weight loss, or repeated infections leading to fever[4].

Bone marrow examination not only helps in final diagnosis but can also help in indicating the approach to diagnosis based on various parameters like cellularity (hypocellular or hypercellular), Blasts (for leukemias), abnormal cells (lymphoma, plasma cells, carcinoma cells, histiocytes), organisms (fungus, parasite), dysplastic changes in cells (MDS) or megaloblastic maturation.

Correlation with bone marrow biopsy is also important in cases where aspirate is hemodiluted or in hypocellular marrows. Biopsy also helps in many conditions which focally involve the bone marrow like metastatic carcinomas or lymphomas or tuberculosis.

This study is performed at a tertiary care centre and medical college in India and is intended to look at BM findings in cases of pancytopenia so that one should keep in mind various differentials that can present with pancytopenia.

Materials and Methods

This was a retrospective study performed at a tertiary care centre and medical college over a period of three years in Department of pathology. Laboratory data from all the cases who presented with pancytopenia (hemoglobin< 10gm/dl total leukocyte count < 4000/mm^3 and platelet count /150,000/mm^3) were retrieved. Clinical details were obtained from patient's case file and was tabulated, analyzed and correlated with that of laboratory parameters. Cases of

chemotherapy induced pancytopenia (whether benign or malignant) were excluded from this study. Bone marrow aspiration was performed from posterior superior iliac spine. Slides were prepared and stained with leishman stain. Biopsy was processed as per laboratory protocol for bone marrow. Special stains were performed wherever required.

Results

In our institute we receive a total of 610 bone marrow specimens over 3 year duration of which we studied around 156 cases who presented with pancytopenia (Table 1). Male: female ratio was 1.6:1 with 97 males and 59 females. The age of the patients ranged from 2 months to 70 years. Out of 156 cases of pancytopenia, 41 patients (26.3%) were in pediatric age group (<18 years) and remaining 115 patients (73.7%) were adults (>18 years).

Most common presentation (Table 2) was pallor (70.5%) followed by fever (30.1%), splenomegaly (23.1%), hepatomegaly (19.8%) and associated lymphadenopathy (17.3%) while only 5.7% cases were asymptomatic.

Peripheral smear findings (Table 3) in most of the cases show presence of anisocytosis (41%) followed by lymphocytosis (32.1%), nucleated red blood cells (31.4%), and poikilocytosis (20.5%). Blasts were seen in 15.4% cases.

Table 1: Bone marrow aspiration findings in pancytopenia (n= 156)

Diagnosis	Total number of cases				Total
	<18 year		>18 year		
	Male	Female	Male	Female	
Megaloblastic anemia	6	4	20	10	40 (25.6%)
Acute leukemias	5	4	14	2	25(16%)
Hypoplastic marrow	8	1	5	8	22(14%)
Metastasis	1	0	7	6	14(8.9%)
Myelodysplastic syndrome	0	0	3	8	11(7.1%)
Lymphoma infiltration	0	0	8	1	9(5.7%)
Plasma cell dyscrasia	0	0	3	3	6(3.8%)
Viral	1	1	1	0	3(1.9%)
Hypersplenism	0	1	1	1	3(1.9%)
Autoimmune (ITP, SLE)	0	2	0	1	3(1.9%)
Hairy cell leukemia	0	0	2	0	2 (1.2%)
Haemophagocytic syndrome	0	0	2	0	2(1.2%)
Myelofibrosis	0	0	1	1	2(1.2%)
Septicemia	0	0	1	1	2(1.2%)
Leishmaniasis	0	0	1	0	1 (0.6%)
Histoplasmosis	0	0	1	0	1(0.6%)
Malaria	0	0	1	0	1(0.6%)
Gauchers Disease	0	1	0	0	1(0.6%)
Tuberculosis	1	0	0	0	1(0.6%)
Hemoglobinopathy	0	1	0	0	1(0.6%)
Inconclusive	3	1	1	1	6(3.8%)
Total	25	16	72	43	156

Table 2: Clinical findings in cases of pancytopenia

Diagnosis	Pallor	Fever	Petechiae	lymphadenopathy	Splenomegaly	Hepatomegaly	Asymptomatic
Megaloblastic anemia (40)	40	1	0	0	0	0	0
Acute leukemias (25)	20	15	2	12	20	24	0
Hypoplastic marrow (22)	22	13	2	0	0	0	1
Metastasis (14)	0	0	0	0	0	0	2
Myelodysplastic syndrome (11)	3	0	0	0	2	2	0
Lymphoma infiltration (9)	6	2	0	9	0	0	0
Plasma cell dyscrasia (6)	2	1	0	0	0	0	3

Viral (3)	0	3	0	2	0	0	0
Hypersplenism(3)	3	0	0	0	3	0	0
Autoimmune (ITP, SLE) (3)	3	1	0	0	0	0	0
Hairy cell leukemia (2)	2	0	0	1	2	0	0
Haemophagocytic syndrome(2)	2	2	0	0	2	1	0
Myelofibrosis(2)	2	1	0	0	2	2	0
Septicemia (2)	0	2	0	0	0	0	0
Leishmaniasis (1)	0	1	0	0	1	1	0
Histoplasmosis(1)	1	1	0	1	1	0	0
Malaria (1)	1	1	0	0	1	0	0
Gauchers Disease (1)	1	0	0	1	1	1	0
Tuberculosis (1)	0	1	0	1	0	0	0
Hemoglobinopathy (1)	1	0	0	0	0	0	0
Inconclusive (6)	1	2	0	0	1	0	3
Total (156)	110 (70.5 %)	47(30.1%)	4 (2.5%)	27 (17.3%)	36 (23.1%)	31 (19.8%)	9 (5.7%)

Table 3: Peripheral blood findings in cases of pancytopenia

Diagnosis	Anisocytosis	Poikilocytosis	Nucleated RBC's	Blasts	Lymphocytosis
Megaloblastic anemia (40)	35	25	15	0	0
Acute leukemias (25)	10	2	10	23	0
Hypoplastic marrow (22)	0	0	3	0	20
Metastasis (14)	10	0	10	0	4
Myelodysplastic syndrome (11)	1	0	6	1	0
Lymphoma infiltration (9)	0	0	0	0	7
Plasma cell dyscrasia (6)	0	0	0	0	6
Viral (3)	0	0	0	0	3
Hypersplenism(3)	3	3	0	0	0
Autoimmune (ITP, SLE) (3)	0	0	0	0	3
Hairy cell leukemia (2)	0	0	0	0	2
Haemophagocytic syndrome(2)	0	0	2	0	0
Myelofibrosis(2)	0	0	0	0	2
Septicemia (2)	1	0	1	0	0
Leishmaniasis (1)	0	0	0	0	0
Histoplasmosis(1)	0	0	1	0	0
Malaria (1)	1	1	0	0	0
Gauchers Disease (1)	0	0	0	0	1
Tuberculosis (1)	1	0	0	0	1

Hemoglobinopathy (1)	1	1	0	0	0
Inconclusive (6)	1	0	1	0	1
Total (156)	64 (41%)	32 (20.5%)	49 (31.4%)	24 (15.4%)	50 (32.1%)

Discussion

Pancytopenia is a common hematological finding seen in many diseases and diagnosis still remains a challenge for pathologist as well as to clinician. Accurate diagnosis is very crucial for management of patient. Bone marrow examination is very important investigation in patients of pancytopenia and should be looked carefully to achieve proper diagnosis. Even in the absence of a final diagnosis, BME can help clinician in approach to diagnosis and management of the patient.

In our study, out of total 610 cases of BME performed, 25.6% cases presented with pancytopenia which is slightly higher than that in literature.[5-7]

Male: Female ratio in our study was 1.6:1 which is comparable to some studies[6,8] while few study showed slightly female preponderance[9].

In this study most common isolated cause of pancytopenia was megaloblastic anemia which is comparable to many studies performed[8,10-13] while few studies found hypoplastic marrow as the most common cause of pancytopenia[6,14-16].

In a study[17], they found neoplastic diseases as most common cause of pancytopenia. In our study also, combined total of all neoplastic cases exceed that of megaloblastic anemia because this medical college has a separate cancer unit that caters predominantly to cancer patients and many cancers when involve bone marrow, presents with pancytopenia.

In our study second most common cause was acute leukemia which includes both acute myeloid and acute lymphoblastic leukemias. Blasts were seen in peripheral blood smears in 23 cases while two showed absence of blasts on PBS (aleukemic leukemia). These two cases turned out to be acute promyelocytic leukemia (APML) with few promyelocytes on PBS and around 80% promyelocytes and 10% blasts on BME. Out of 23 cases, 8 cases showed mildly reduced count with few blasts on PBS (5-10%) and bone marrow in all these cases show features of acute leukemia with > 50% blasts.

Hypoplastic marrow was 3rd most common cause and all these cases were confirmed on biopsy. Majority of these cases (20) show reduced count with predominantly lymphocytes on peripheral blood smears and similar findings on BME. The diagnosis was confirmed on bone marrow biopsy and was in correlation with aspirate findings.

In our study metastasis of solid tumors (Fig. 1) was seen as reason for pancytopenia in 14 cases with lung, breast and prostate as the most common site of primary in adults while in a single pediatric case ewing's sarcoma was the primary tumor producing pancytopenia. In most of these cases (10) peripheral blood showed circulating nucleated RBC's.

In this study, Myelodysplastic syndrome was found as a cause of pancytopenia in 11 cases, lymphoma infiltration in 9 cases and marrow plasmacytosis in 6 cases.

We found 2 cases of hairy cell leukemia presenting with pancytopenia and one was diagnosed outside as hypocellular marrow with marrow fibrosis on biopsy. He was referred to our hospital with worsening symptoms and marrow was repeated and showed hypocellular marrow with atypical lymphoid cells (Fig. 2). Flow cytometry was asked for and it showed features of Hairy cell leukemia. This is important to discuss that irrespective of myelofibrosis on biopsy, if atypical lymphoid cells are seen on aspirate; special investigations like flow cytometry must be performed as Hairy cell leukemia can frequently cause bone marrow fibrosis.

We found 2 cases presented to us with pancytopenia, persistent fever, splenomegaly. On laboratory work up one case showed blood culture positive for pseudomonas and other patient was a known case of carcinoma ovary with suspected metastasis to bone marrow in view of decreasing counts. Bone marrow from both these cases showed scattered histiocytic cells showing hemophagocytosis (Fig. 3). No metastasis was found in cases suspected of metastatic carcinoma. In view of significant histiocytes showing hemophagocytosis serum ferritin was asked for and was raised in both the cases. Thus, the final diagnosis was made as hemophagocytic syndrome (HPS) as these cases fulfilled 5 criteria of the hemphagocytic syndrome as mentioned in literature[18]. One patient succumbed to the disease irrespective of treatment. It is important to discuss that this is a very severe disease and prognosis and survival is very poor if treatment is not initiated early. Thus, patient with presence of hemophagocytosis in BM should be evaluated for HPS.

Other causes which we found as a cause of pancytopenia were viral induced, autoimmune (idiopathic thrombocytic purpura- 2cases and systemic lupus erythematosus- 1 case), myelofibrosis, septicemia, leishmaniasis (Fig. 4), histoplasmosis (Fig. 5), Hypersplenism, malaria, tuberculosis, Gaucher's disease (Fig. 6) and thalassemia.

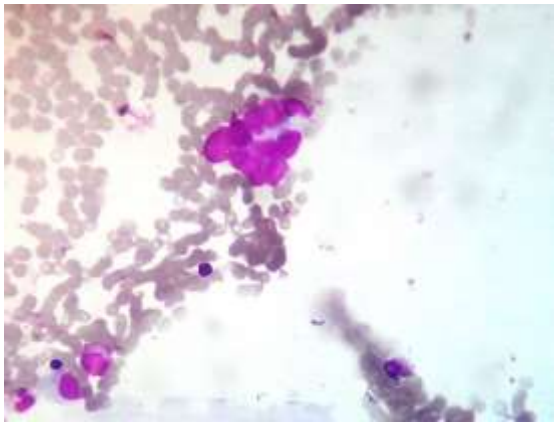

Fig. 1: Smears showing clusters of small round cells in a known case of small cell carcinoma (BM, 400x)

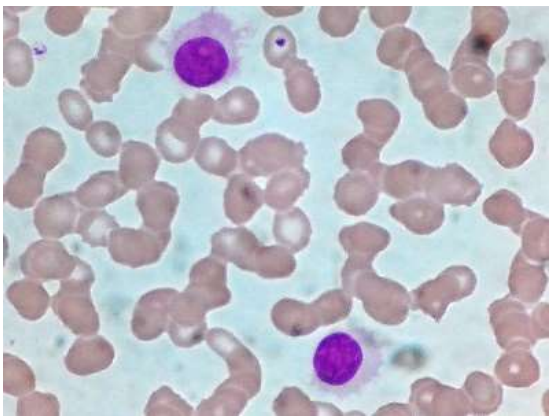

Fig. 2: Hypocellular marrow showing scattered atypical lymphoid cells with cytoplasmic projections (BM, 1000x)

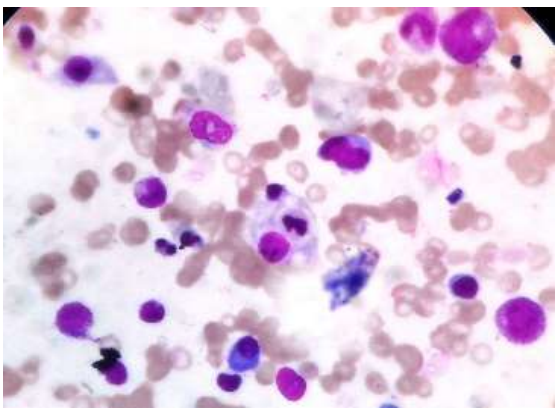

Fig. 3: Histiocytic cells showing phagocytosis of nucleated red blood cells (BM, 1000x)

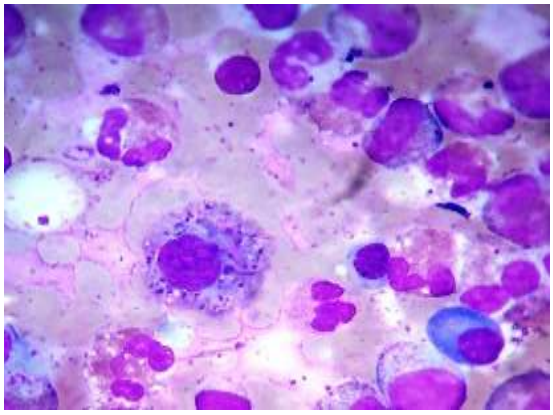

Fig. 4: Scattered and intra-cytoplasmic parasite consistent with leishmaniasis (BM, 1000x)

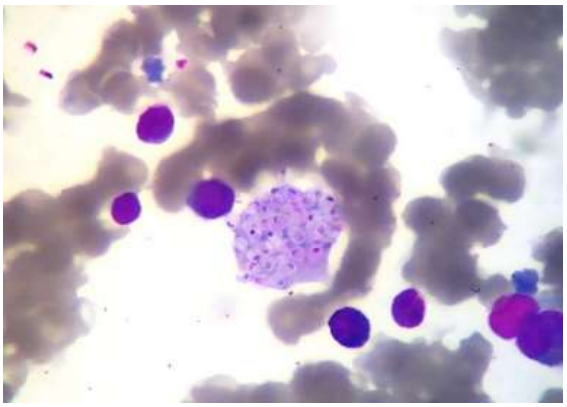

Fig. 5: Cytoplasmic fragment showing intracellular histoplasma organisms (BM, 1000x)

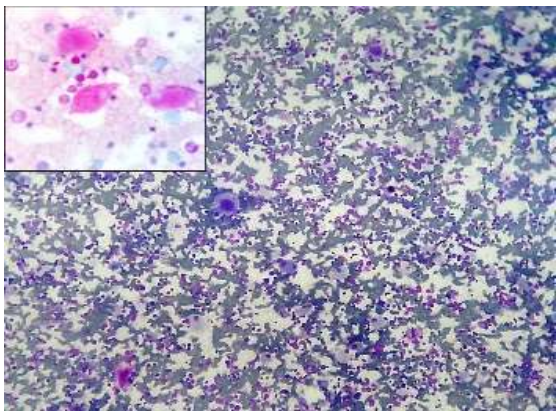

Fig. 6: Gaucher's cells with inset showing PAS positive intacellular accumulation (BM, 1000x)

Conclusion

Bone marrow examination is an important investigation to be performed in cases of pancytopenia. Diagnosis can be made in majority of cases and in few cases it can direct the clinician to approach the disease. Most common cause of pancytopenia are megaloblastic anemia, leukemias and lymphomas, hypoplastic marrow and metastasis. In addition, specific causes of pancytopenia (e.g. Hemophagocytic syndrome, storage disorders, Hairy cell leukemia, fungal or parasitic

infections) should be kept in mind as some of them can be life threatening. Correlation of clinical, peripheral smear finding and bone marrow aspirate findings are required to arrive at final diagnosis.

Conflicts of interest: Nil

References

1. Ishtiaq O, Baqai HZ, Anwer F, Hussain N J. Patterns of pancytopenia patients in a general medical ward and a proposed diagnostic approach. Journal of Ayub Med Coll Abbottabad. 2004 Jan-Mar;16(1):8-13.
2. Tilak V, Jain R. Pancytopenia--a clinico-hematologic analysis of 77 cases. Indian J Pathol Microbiol. 1999 Oct;42(4):399-404.
3. Williams MD. Pancytopenia, aplastic anemia and pure red cell aplasia. In: Lee RG, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, (eds). Wintrobe's Clinical Haematology 10th edn. Williams and Wilkins; 1997. pp1449-76.
4. Santra G, Das BK. A cross-sectional study of the clinical profile and aetiological spectrum of pancytopenia in a tertiary care centre. Singapore Med J. 2010 Oct;51(10):806-12.
5. Pathak R, Jha A, Sayami G. Evaluation of bone marrow in patients with pancytopenia. Journal of Pathology of Nepal 2012;2:265 -71.
6. Jha A, Sayami G, Adhikari RC, Panta AD, Jha R. Bone Marrow Examination in Cases of Pancytopenia. J Nepal Med Assoc. 2008;47:12-7.
7. Bashawri LA. Bone marrow examination. Indications and diagnostic value. Saudi Med J 2002;23:191-6.
8. Das Makheja K, Kumar Maheshwari B, Arain S, Kumar S, Kumari S, Vikash. The common causes leading to pancytopenia in patients presenting to tertiary care hospital. Pak J Med Sci. 2013;29:1108–11.
9. Aziz T, Liaquat Ali L, Ansari T, Liaquat HB, Shah S, Jamal AJ. Pancytopenia: Megaloblastic anemia is still the commonest cause. Pak J Med Sci. 2010;26:1132-6.
10. Khunger JM, Arulselvi S, Sharma U, Ranga S, Talib VH. Pancytopenia – A clinico haematological study of 200 cases. Indian J Pathol Microbiol. 2002;45:375–9.
11. Khodke K, Marwah S, Buxi G, Vadav RB, Chaturvedi NK. Bone marrow examination in cases of pancytopenia. J Acad Clin Med. 2001;2:55–9.
12. Tilak V, Jain R. Pancytopenia – A clinico-hematologic analysis of 77 cases. Indian J Pathol Microbiol.1999;42: 399–404.
13. Gayathri BN, Rao KS. Pancytopenia: A clinico hematological study. J Lab Physicians. 2011;3:15–20.
14. Kumar R, Kalra SP, Kumar H, Anand AC, Madan H. Pancytopenia – A six year study. J Assoc Physicians India. 2001;49:1078–81.
15. Dasgupta S, Mandal PK, Chakrabarti S. Etiology of Pancytopenia: An observation from a referral medical institution of Eastern Region of India . J Lab Physicians. 2015;7:90-5.
16. Hossain MA, Akond AK, Chowdhary MK, Sikder AM, Rashid MA, "Pancytopenia-A study of 50 cases", Bangladesh Journal of Pathology. 1992;1:9-12.
17. Keisu M, Ost A. Diagnosis in patients with severe pancytopenia suspected of having aplastic anemia. Eur J Haematol. 1990;45:11-4.
18. Henter JI[1], Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48 (2):124-131.