The Professional Medical Journal
www.theprofesional.com

DOI: 10.29309/TPMJ/18.4500

ORIGINAL PROF-4500

HAEMATOLOGICAL DISORDERS;

ANALYSIS OF HEMATOLOGICAL DISORDERS THROUGH BONE MARROW BIOPSY EXAMINATION.

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Article received on:
10/11/2017
Accepted for publication:
10/03/2018
Received after proof reading:
02/06/2018

ABSTRACT… Objectives: To analyse the pattern of hematological disorders through bone marrow aspiration, and to compare the final diagnoses with their referral diagnoses made by the referring physicians.**Study Design:** Cross sectional descriptive study. **Period:** 1st January -2016 to 30th December-2016. **Setting:** Department of Pathology, Khyber Teaching Hospital, Peshawar. **Materials and Methods:** 352 patients were included in the study. Bone marrow diagnosis was recorded. Data was analysed by SPSS version 18 and results were drawn accordingly. **Results:** A total of 352 patients underwent bone marrow aspiration during the study period. About 15 patients had diluted bone marrow aspirates. So, they were excluded from the study. The remaining 337 patients were included in the study. The age of the study sample ranged from 9 months to 72 years (mean age 36 years ±17.8 SD). There were 185 (55%) male and 151 (45%) females. Male to female ratio was 1.2:1. The commonest indication for bone marrow aspiration was "suspected malignancy", which was suspected in 114(33.85) patients, followed by "pancytopenia", which was seen in 69(20.55%) patients. About 69 (20.5%) patients were referred for work up of anemia. Bicytopenia was seen in 69(20.5%). The bone marrow aspiration showed that megaloblastic anemia was the commonest disorder observed in 37(10%) cases. Second common disorder was acute lymphoblastic leukemia, that was seen in 31 (9%) patients, followed by acute myeloid leukemia, which was seen in 26(7.7%) cases. Hemolytic anemia was seen in 20 (15.9%) cases. Aplastic anemia was seen in 18 (5.3%) cases. Multiple myeloma and mononuclear infiltration was seen in 17 (5%) patients each. Anemia of chronic disorder was seen in 16(4.7%) cases. Idiopathic Thrombocytopenic Purpura was seen in 12 (3.6%) patients. Iron deficiency anemia was seen in 11 (3.3%) patients. Chronic Lymphocytic Leukemia was seen in 10 (2.9), Mixed deficiency anemia in 9 (2.7%), Myelodysplasia in 6 (1.7%), Malaria in 5(1.5%), and Niemann Pick in 4 (1.2%) patients. Gaucher disease and Visceral Leishmania was seen in 2 (0.6%) patients each. Histiocyticlymphohistiocytosis and Chediak Hegashi syndrome was seen in 1 (0.3%) patients each. **Conclusions:** Megaloblastic anemia, Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Hemolytic Anemia and Aplastic Anemia are the common hematological disorders in our set up. Bone marrow is a reliable procedure to diagnosis hematological diseases when routine investigations fail to make diagnosis.

Key words: Bone Marrow Aspiration, Haematological Disorders, Hemolytic Anemia, Aplastic Anemia, Megaloblastic Anemia, Leukemia.

Article Citation: Khan MI, Ahmad N, Fatima SH. Haematological disorders; analysis of hematological disorders through bone marrow biopsy examination. Professional Med J 2018; 25(6):828-834.
DOI:10.29309/TPMJ/18.4500

INTRODUCTION

Haematological disorders are quite common in general population.[1,2] These disorders may range from simple conditions like iron deficiency anemia to infiltrative caricnomas involving the bone marrow.[3-6] Majority of these diseases need bone marrow aspiration examination for definitive diagnosis.[4,6] There are a number of disorders in paediatric population which need the bone marrow biopsy examination for their diagnosis, like Gauchers disease and Niemann Pick disease.[6] Tumors that infiltrate the bone marrow also need bone marrow aspiration examination fordiagnosis.[6]

Bone marrow aspiration and biopsy plays an important role in diagnosing haematological diseases.[1,2,3,4,5] Sometimes, the hematological disorders present with vague symptoms.[6] In such cases, the clinicians face a problem to reach to

final diagnosis.[1,6] So, clinicians advise the bone marrow examination in order to reach the final diagnosis and decide further management of the patients.[6,7] Bone marrow aspirate findings are interpreted in the light of patient's history, examination and laboratory findings; and final diagnosis is made.[2]

Pancytopenia, Megaloblastic anemia, Aplastic anemia, Idiopathic thrombocytopenia purpura and Hepatosplenomgaly are a few commonly seen conditions in which the bone marrow biopsy is advised by the clinician.[1,6] In Megaloblastic anemia, the hemoglobin level is low and Mean cell volume is raised above normal values.[1] Megaloblastic anemiais caused due to deficiency of Vitamin B-12 and folate.[1,8] Serum vitamin B-12 and folate levels should be donein patients who present with pancytopenia and are suspected of having megaloblastic anemia.[1,9] Idiopathic thrombocytopenic pupura is an autoimmune disorder that is caused due to auto antibodies that are formed against the platelet antigen, resulting in the destruction of platelets.[1] The platelet count is below normal, but the bone marrow megakaryocytes are increased in such patients.[1,3] Patients with hepatosplenomegaly usually have underlying malignancies like leukemia.[1] Leukemia is a common hematological malignant disorder in children and bone marrow examination is necessary for making its diagnosis.[6]

The pattern of hematological disorders is different in the western countries and the developing world.[6] The data regarding pattern of hematological disorders in the developed countries may not be representative of our population. Therefore, this study was conducted with the aim to analyse the pattern of haematological disorders on bone marrow examination in our setup.

MATERIALS AND METHODS

This Cross-sectional Descriptive study was performed at the Department of Pathology, Khyber Teaching Hospital, Peshawar, from 1st January 2016 to 31st December 2016. Non probability purposive sampling technique was used. Demographic data of patients was noted including age, sex and indication for bone marrow. Bone marrow aspiration was done under local anasthesia. Bone marrow sample was obtained from anterior tibial tuberosity in children less than two years age, and posterior tibial tuberosity in patients above two years age. The area was cleaned with alcohol swab, local anesthesia was given. After two minutes, aspiration sample was taken using 21 gauge LP needle. If aspirate was suspected to be dilute, trephine biopsy was taken in the same sitting. Slides were stained using Wrights stain, and Prussian blue stain for iron. Slides were examined under microscope, and findings were recorded. Results were analysed using SPSS version 18. Mean and standard deviation were calculated for quantitative variables e.g. age. Frequencies and percentages were calculated for qualitative variables like diagnosis and gender.

Inclusion Criteria

Patients of all ages and both sexes, for whom bone marrow biopsy was advised by their consultants were included in the study.

Exclusion Criteria

Patients whose bone marrow samples were diluted (showing no heamatopoeitic cells) were excluded from the study.

RESULTS

A total of 352 patients were subjected for bone marrow biopsy. About 15 patients had diluted aspirate samples, and hence they were excluded from the study. Remaining 337 patients were included in the study. The age range of study sample ranged from 9 months to 72 years (mean age 36 years ±17.8 SD). There were 185 (55%) male and 151 (45%) females. Male to female ratio was 1.2:1.

Table-I shows the "referral diagnosis" in patients i.e the diagnoses suspected by the physician, for which the patients were referred for bone marrow biopsy (Panel A), and the "final diagnosis" of hematological disorders made on bone marrow aspiration findings (Panel B). Table-II compares the "referral diagnoses" with the "final bone marrow diagnoses".

PUO: pyrexia of unknown origin, ITP:

Immune thrombocytopenia purpura. MPD: Myeloproliferative disorders. CDA: congenital dysplastic anemia, HLH: Hemophagocytic Lymphohistiocytosis.

PANEL-A	PANEL-B
Referral diagnosis/indications :n(%)	**Final Bone Marrow diagnosis: n (%)**
Suspected hematological malignancy :114(33.8) Pancytopenia:69(20.5%) Anemia work up:50 (14.8%) Bicytopenia (low Hb. and platelets):24 (7.1%) Suspected Lymphoma:15 (4.5%) Suspected ITP: 15 (4.5%) Suspected Multiple myeloma: 14 (4%) PUO/unknown diagnosis: 9(2.7%) Suspected Megaloblastic anemia: 8(2.4%) Suspected Aplastic anemia: 5(1.5%) Suspected Polycythemia Vera: 4(1.2%) Suspected Storage disorder:3 (0.9%) Suspected MPD: 3 (0.9%) Suspected CDA: 2 (0.6%) Suspected Malaria: 1 (0.3%) Metastatic disease: 1 (0.3%)	Megaloblastic anemia: 37(10.9%) Excessive Peripheral Desruction:32(9.4%) Acute Lymphoblastic Leukemia:31(9.1%) Normocellular marrow:31(9.1%) Acute Myeloid Leukemia:26(7.7%) Hemolytic anemia :20(5.9%) Aplastic anemia:18(5.3%) Multiple myeloma:17(5%) Mononuclear infiltration:17(5%) Anemia of chronic disorder:16(4.7%) ITP:12(3.6%) Iron deficiency anemia:11(3.3%) Chronic Lymphocytic Leukemia:10(2.9%) Mixed deficiency anemia:9(2.7%) Myelodysplastic syndrome:6(1.7%) Chronic Myeloid Leukemia:8(2.4%) Polycythemia vera:6(1.7%) Essential thrombocythemia:5(1.5%) Myelofibrosis:5(1.5%) Hypereisinophilic syndrome:5(1.5%) Malaria:5(1.5%) Nieman pick disease:4(1.2%) Gaucherdisease:2(0.6%) Visceral leshmeniasis:2(0.6%) Chediakhegashi syndrome:1(0.3%) HLH:1(0.3%)

Table-I. Suspected 'referral diagnosis' and 'Final Diagnoses' in 337 cases.

DISCUSSION

Most of the hematological disorders present with very vague symptoms and thus, pose a diagnostic challenge for the clinicians.[1] Bone marrow aspiration biopsy proves very helpful in such cases.[6] It not only gives final diagnosis but also guides the further management of the patients.[1]

In the present study, it was found that most common suspicion for which bone marrow biopsy was advised were hematological malignancy, pancytopenia, anemia and bicytopenia. Bone marrow examination was of importance in giving conclusive diagnosis for these indications and helping clinicians decide further management plan.

The commonest hematological disorder in the present study was Megaloblastic anemia, which was seen in 37(10.9%) patients. In a local study done by Munir and collegues, megaloblastic anemia was seen in 16.6% of patients.[1] In another study done by Shiddappa, megaloblastic anemia was present in 27% of the patients.[10] These values are high as compared to the present study. In another study done by Khan A, megaloblastic anemia was present in 14.6% of the cases.[6] This figure is somewhat close to the one in the present study. Megaloblastic anemia is one of the causes of pancytopenia.[6]

Excessive peripheral destruction of haematopoietic cells was seen in 32 (9.4%) patients in the present study.

These patients had no atypical cells in their peripheral blood smear. Bone marrow was hypercellular with no blast cells. So bone marrow failure and leukemia was ruled out by bone marrow aspirate findings.

Referral diagnosis	Number of patients	Final diagnosis	Number of patients
Suspected Hematological malignancy	114	Leukemias Anemias Normocellular marrow Bone marrow Infiltration Myeloproliferative neoplasms Idiopathic Thrombocytopenic Purpura Malaria Leishmania	46 22 21 7 12 3 1 1
Pancytopenia	69	Anemias Normocellular marrow Bone marrow infiltration Myelodysplasia Myeloproliferative disorders Malaria Leukemias Storage disorders Visceral leishmaniasis	23 19 7 3 3 3 5 5 1
Anemia (work out)	50	Anemias Normocellular marrow Multiple myeloma Myeloproliferative disorders Leukemias Myelodysplasia Storage disorders	25 10 3 3 5 2 2
Bicytopenia (low Hb. and platelets)	24	Anemias Bone marrow infiltration Normocellular marrow Myelodysplasia Leukemias	14 6 2 1 1
Suspected Lymphoma	15	Leukemias Multiple myeloma Anemias Normocellular marrow	9 1 2 3
Suspected Immune Thrombocytopenic Purpura	15	Idiopathic Thrombocytic Purpura Normocellular marrow Anemias	9 5 1
Suspected Multiple myeloma	14	Multiple myeloma Anemias	9 5
Pyrexia unknown origin/ Unknown diagnosis	9	Myeloproliferative disorders Anemias Multiple myeloma Leukemias Malaria	2 2 2 2 1
Suspected Megaloblastic anemia	8	Anemias Normocellular marrow	7 1
Suspected Aplastic anemia	5	Aplastic anemia	5
Suspected Polycythemia Vera	4	Polycythemia Vera	4
Suspected storage disorder	3	Iron deficiency anemia Chediakhegashi syndrome Normocellular marrow	1 1 1
Suspected MPD	3	Chronic Myeloid Leukemia	3
Suspected CDA	2	Hemolytic anemia	2
Suspected Malaria	1	Hemolytic anemia	1
Metastatic disease	1	Chronic Myeloid Leukemia	1

Table-II. Comparison of referral diagnosis and final diagnosis made on bone marrow biopsy examination (n=337)
MPD: Myeloproliferative disorders, CDA: Congenitaldysery thropoietic anemia.

Pooling of blood cells occur in hyperactive spleen which results in pancytopenia in the peripheral blood.[11] In a local study done by Munir and collegues, excessive peripheral destruction was seen in 3.2% of the patients.[1] In a study done in King Fahad Hospital Saudi Arabia, 4.4% of the patients were diagnosed as having excessive peripheral destruction.[12]

Next common hematological disorder was Acute Lymphoblastic Leukemia (ALL), which was seen in 31 (9.1%) cases. Acute Myeloid Leukemia (AML) was seen in 26 (6.6%) cases. Thus, it was second commonest leukemic disorder next to ALL in the present study. In one study, ALL was present in 11.3% of the cases.[6] Similar results are reported in another studies done in Peshawar.[1,5,13] ALL is the commonest malignant disorder of childhood.[6] The exact etiology of ALL is not known.[1,6] However, exposure to pesticides, viral infection and exposure to radiation are thought to be responsible for causing leukemia.[6]

Bone marrow aspirate was normal in 31 (9.1%) cases. Thus bone marrow examination helps in diagnosing as well as ruling out hematological disorders. In a study done by Addo and collegues in Ghana, about 8.75% of the patients had a normal bone marrow.[2]

Aplastic anemia was seen in 18 (5.3%) cases in the present study. The bone marrow aspirate was hypocellular. Trephine showed increased fat spaces with dispersed lymphocytes and plasma cells. Clinicians were advised to rule out any viral etiology and stop any offending drug which may be causing bone marrow aplasia. Aplastic anemia may be congenital or acquired[1,14], Failure of the bone marrow results in decreased production of blood cells.[14] Such patients present with pallor, fever and bruises all over the body[6].Viral infections and drugs are common causes of acquired Aplastic anemia.[15] Hepatitis is a common cause of Aplastic anemia in our society.[15,16,17]

Idiopathic Thrombocytopenic Purpura (ITP) was seen in 12(3.6%) cases in the present study. There was low platelet count, but bone marrow showed increased megkaryocytes, the finding suggestive of ITP.[18] Monitoring of platelet count was advised in such patient. In one study done by Munir and collegues, ITP was seen in 16.6% of patients.[1] This is much higher than that reported in the present study. Similar findings were presented by other local and international studies.[3,6,18,19] Patients with ITP present with epistaxis and bruises all over body.[20] A trial of corticosteroids usually improve the condition.[20]

Iron deficiency anemia was seen in 11(3.35%) cases in the present study. Bone marrow iron stores were absent which is typical of iron deficiency anemia.[21,22] In a study conducted in Peshawar, about 5.7% patients had iron deficiency anemia.[1] This figure is somewhat cose to the present study. In another study done by Khan A., about 7.6% paients had iron deficiency anemia.[6] Similar data was presented in a study of Ikram N. from Islamabad.[23]

Myelofibrosis was seen in 5(1.5%) cases in the present study. In this disorder, the megakaryocytes in the bone marrow produces platelet-derived growth factor, which causes fibrosis of the bone marrow.[1] Fibrous tissue replaces the normal hemopoietic tissue and produces pancytopenia.[1] In a study done by Munir and collegues, myelofibrosis was seen in only 0.6% of the patients[1].In a study conducted in Ghana, myelofibrosis was present in 2.5% of the patients.[2] This figure is somewhat close to that in the present study.

Visceral leishmaniasis was diagnosed in 2 (0.6%) cases in the present study. Bone marrow aspiration showed amastigote forms of Leishmania Donovani bodies. Higher incidence of 6.6% was reported in two local studies.[5,6] In a study done in Peshawar, only 0.5% patients had visceral leishmaniasis.[1] In a similar study done by Niazi M at Lady Reading Hospital Peshawar, only 0.2% patients had visceral leishmaniasis.[24] This is in accordance with the present study. Patients suspected of having visceral leishmaniasis present with pallor, fever and visceromegaly.[25] Bone marrow aspiration is very yielding in such cases.[25]

By analyzing all the data, it was found that megaloblastic anemia is the commonest non-malignant hematological disorder in our setup, while ALL is the commonest malignant hematological disorder, followed by AML. Proper education and awareness of population regarding the causation, prevention and treatment of these diseases is warranted. This will help improve the health of community and reduce morbidity. It was also found that bone marrow plays very important role in making final diagnosis in patients with vague clinical signs and symptoms. It helps physician decide further management plan of the patients. Hence bone marrow biopsy is an important diagnostic tool.

CONCLUSION

Megaloblastic Anemia was the commonest nonmalignant hematological disorders in our setup. Acute lymphoblastic leukemia was the most common malignant hematological disorders, followed by Acute Myeloid Lekemia. Proper education and awareness of population regarding the causation, prevention and treatment of these diseases may improve health of community and reduce morbidity. The study has also demonstrated that bone marrow biopsy examination is a reliable procedure to diagnose different hematological diseases in cases where routine investigations fail to make conclusive diagnosis.

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2	Neelam Ahmad	Data analysis, Result compilation.	
3	Syeda Hina Fatima	Literature review, Proof reading, Discussion.	