Bone Marrow Examination in Elderly Patients at Tribhuwan University Teaching Hospital.

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Article received: 3rd Aug 2021
Article accepted: 29th Dec, 2021

ABSTRACT

Introduction: Bone marrow examination is an important investigation for diagnosis of hematological and nonhematological disorders. There is an increase in the elderly population and frequency of diseases among them for which bone marrow examination is indicated. Hence, bone marrow examination in elderly population requires special attention.To evaluate bone marrow findings in elderly patients (65 years of age and above) at a tertiary care hospital.

Materials and methods: This was a hospital-based, observational, cross-sectional study of elderly patients undergoing bone marrow examination at the department of pathology, Tribhuwan University Teaching hospital from May 2018 to April 2019. Morphology of bone marrow aspiration and biopsy were studied in these cases and correlated with clinical and other ancillary laboratory tests parameters.

Results: The most common indication of bone marrow examination was pancytopenia (23.72%) followed by suspected plasma cell neoplasm (23%) and suspected acute leukemia (16%). AML (15%) was the most common neoplastic disorder followed by myeloproliferative neoplasm (13.6%), myelodysplastic syndrome (10%) and multiple myeloma (8%). Anemia due to renal failure (8%) was the most common non neoplastic disorder followed by megaloblastic anemia and anemia of chronic inflammation (5% each).

Conclusion: Neoplastic disorders were more common than nonneoplastic and hematological malignancies were the most common diagnosis. Bone marrow examination alone was able to yield specific diagnosis in the majority of cases. The diagnostic yield of bone marrowexamination increased further by correlating bone marrow findings with clinical parameters and other ancillary tests.

Keywords: Bone marrow examination; diagnosis; elderly; indications.

INTRODUCTION

Bone marrow examination is a procedure done routinely in the hospitals for the diagnosis and management of hematological as well as nonhematological disorders.Itis a minimally invasive procedure consisting of two most important techniques: aspiration and trephine biopsies which are complementary to each other. In addition to the microscopic evaluation of the cells and the structure, additional tests can be performed depending on the purpose like immunohistochemistry, flow cytometry, cytogenetic and molecular studies.

The elderly population is on rising trend worldwide and in Nepal as well.[1,2,3]WHO has defined elderly as those 65 years of age and above.[4] In elderly population, neoplastic disorders are more common as aging is the main risk factor for the development of cancer.[5]Studies have shown that the probability of being diagnosed with some hematological malignancy increases in individuals over 65 years old.[6] Hence, with the rise in elderly population and more of them undergoing bone examination, bone marrow studies in elderly population holds special significance.

Although there are many studies and literature on bone marrow examinations, not many studies have been conducted on elderly population. The main aim of this study is to identify the common indications for bone marrow examination in elderly populations, 65 years of age and above and to evaluate common bone marrow diagnosis.

MATERIALS AND METHODS

This was ahospital-based, observational, cross-sectional, non-interventional, descriptive studycarried out at the department of pathology, Tribhuwan University Teaching hospital from May 2018 to April 2019. Ethical approval was obtained from Institutional Review Board of the Institute of Medicine.As per WHO's definition of elderly, patients of age 65 years and above, who underwent bone marrow examination at the department of pathology were included in the study. Follow up bone marrow examination of previously diagnosed cases and bone marrow examination done for staging of lymphoma cases were excluded from the study.

Informed consent was obtained from each of the patients prior to the procedure. Under aseptic measures, bone marrow aspiration was done and biopsy was obtained through posterior iliac crest. Salah needle of 16G and Jamshidi needle 11G were used for aspiration and biopsy respectively. Five to six smears were prepared from aspirated marrow and sent to the hematology lab for Wright's stain. Aspirated materials were sent in heparin vial to a referred laboratory for flow cytometry and cytogenetic/molecular studies as per indicated.

Bone marrow biopsy specimen of 1.5-2 cm obtained was collected in a container withBouin's fixativeand sample was submitted to histopathology lab for processing and preparation of Hematoxylin and Eosin-stained sections. Bone marrow aspiration smears and biopsy sections were examined by thetwo pathologists. Clinical history, clinical findings, indications for bone marrow examination, total leucocyte count, hemoglobin level, platelet count, peripheral blood smear findings, bone marrow aspiration findings, bone marrow biopsy findings, ancillary tests such as flow cytometry, cytogenetics/ molecular tests findings and biochemical test results were studied in each case. All the data were entered in Microsoft Excel XP (2010). The results werethen analyzed by IBM SPSS Statistics program, version 20.

RESULTS

During a period of one year, a total of 588 bone marrow examinations were carried out. 59 cases were included in this study as per the inclusion and exclusion criteria. The age range was 65-93 years. The median age was 71 years. 37 cases were male and 22 cases were female with M:F being 1.68:1. Total 59 cases were divided into three age groups: 65-75 years, 76-85 years and above 85 years. Maximum number of cases (76.28%) was seen in the age group 65-75 years.

The most common indication for bone marrow examination in elderly patients was pancytopenia followed by suspicion for plasma cell neoplasm and suspected acute leukemia (Table 1).

Diagnosis was achieved in 44 out of 59 cases following bone marrow examination, clinical correlation and other ancillary tests**.** Hematological malignancies were the most common diagnosis with acute myeloid leukemia constituting 15.05% of total cases. Myelodysplastic syndrome and multiple myeloma were second and third most common hematological malignancies constituting 10.46% and 8.47% of total cases respectively. Non neoplastic disorder constituted 24% of total cases.

Anemia due to renal failure was the most common non neoplastic disorder followed by anemia of chronic inflammation and megaloblastic anemia (Table 3).

Table 1: Indications for Bone Marrow Examination

S. N	Indications	No. of cases (n)	Percentage %
1	Pancytopenia	14	23.72
2	Suspected plasma cell neoplasm	13	22.03
3	Suspected acute leukemia	10	16.90
4	Anemia	09	15.25
5	Suspected Myeloproliferative neoplasm	08	13.55
6	Bicytopenia	03	5.08
7	Thrombocytopenia	02	3.38
	Total	**59**	**100**

Table 2: Bone marrow diagnoses based on combined aspiration and biopsy

S. N.	Diagnoses	No. of cases (%)
1	Acute leukemia	12 (20.33%)
2	Erythroid hyperplasia	7 (11.86%)
3	Myelodysplastic syndrome	6 (10.16%)
4	Multiple myeloma	5 (8.47%)
5	Megaloblastic anemia	3 (5.08%)
6	Essential thrombocythemia	3 (5.08%)
7	Reactive plasmacytosis	3 (5.08%)
8	Chronic myeloid leukemia	2 (3.38%)
9	Polycythemia Vera	2 (3.38%)
10	Megakaryocytic thrombocytopenia	2(3.38%)
11	Lymphocytosis	1 (1.69%)
12	Metastatic carcinoma	1 (1.69%)
13	Hyperplastic marrow	1 (1.69%)
14	Within normal limit	11(18.64%)
Total		**59**

Table 3: Final diagnoses following bone marrow examination and other ancillary tests and distribution by sex

S. N.	Diagnoses	Male	Female	Total cases(%)
1	Acute Myeloid leukemia	05	04	9 (15.25%)
2	Myelodysplastic syndrome	05	01	6 (10.16%)
3	Multiple myeloma	02	03	5 (8.47%)
4	Anemia of Renal failure (ARF)	04	01	5 (8.47%)
5	Anemia of chronic inflammation (ACI)	02	01	3 (5.08%)
6	Megaloblastic anemia	03	00	3 (5.08%)
7	Essential Thrombocythemia	01	02	3 (5.08%)
8	Chronic myeloid leukemia	02	01	3 (5.08%)
9	Polycythemia Vera	02	00	2 (3.38%)
10	Idiopathic thrombocytopenic purpura	01	01	2 (3.38%)
11	B cell Acute lymphoid leukemia	01	00	1(1.69%)
12	Solitary plasmacytoma	01	00	1(1.69%)
13	Chronic lymphoproliferative disorder	01	00	1(1.69%)
14	Metastatic carcinoma	01	00	1(1.69%)
15	Hypersplenism	01	00	13
16	Undiagnosed	05	08	(22.03%)
	Total	**37**	**22**	**59**

Figure 1: Percentage of distribution of different diagnostic categories

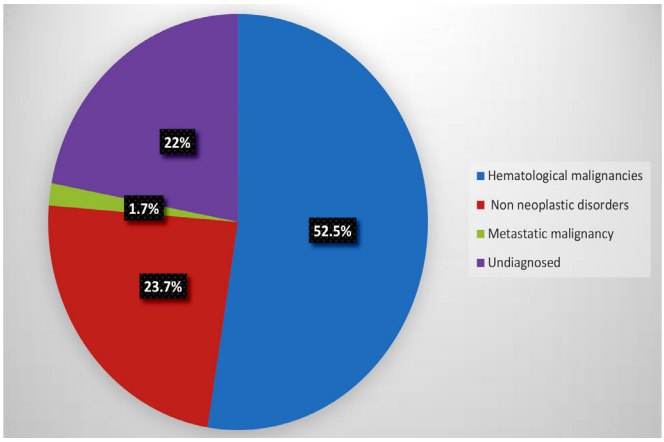


Image 1: Bone marrow aspirate from a patient with Acute myeloid leukemia, NOS with minimal differentiation (Wright stain, Oil immersion)

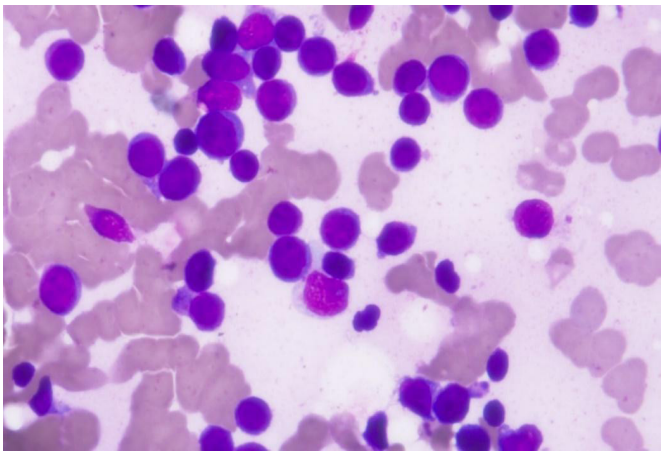
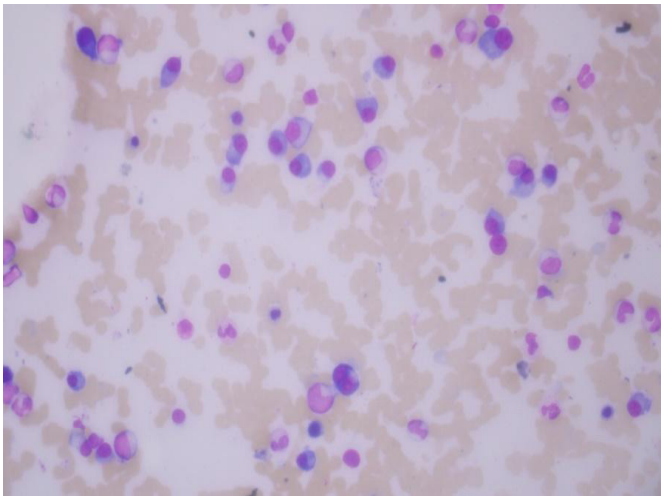
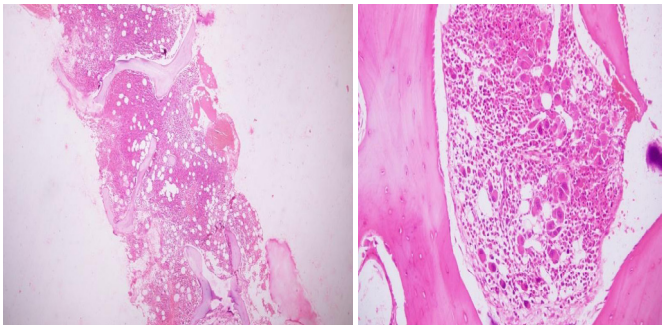


Image 2: Bone marrow aspirate from a patient with Multiple myeloma showing increased plasma cells (Wright stain, 400X)



Images 3: Section of bone marrow trephine biopsy specimen from a patient with Essential thrombocythemia showing increased cellularity (A, paraffin embedded H&E, 40X) and increased proliferation of megakaryocytes (B, paraffin embedded H&E, 200X).



DISCUSSION

In the five years retrospective study conducted by Manion et al on elderly patients of 85 years of age and above, the most common indication was pancytopenia comprising 19% of total cases followed by thrombocytosis or leukocytosis (17%) andanemia (13%). Suspicion of plasma cell myeloma was the fourth commonest indication comprising 10% of total cases.[7] Similar study conducted by Sulakshana et al on elderly patients of 60 years of age and above showed cytopenia (54%) as the commonest indication for bone marrow examination followed by suspicion of plasma cell myeloma (20%) and suspicion of leukemia/ lymphoma (14%).[8]

In the study conducted by Mirzai et al on 1154 cases including all age groups (age ranging from one to 95 years), the most frequent indication was pancytopenia, followed by suspicion of multiple myeloma and lymphoma/leukemia.[9] Study conducted by Ahmed et al on general patient populations showed bicytopenia/pancytopenia (44%) as the commonest indication followed by unexplained anemia (28%) and leukocytosis (9.5%).[10]

On combining aspiration and biopsy findings in our study, 36 out of 59 cases (61%) yielded specific diagnosis which increased to 46 cases (78%) after correlating with clinical and other laboratory parameters. Cases in which specific diagnosis could not be achieved based on bone marrow examination alone were erythroid hyperplasia, reactive plasmacytosis, lymphocytosis, hyperplastic marrow and normal marrow. In these cases, further evaluation was done by correlating with clinical

findings, Perl stain for iron status, serum iron profile, serum vitamin B12 and folate level. Along with these, other biochemical parameters were taken into consideration to reach a final diagnosis in these patients.Meanwhile, thirteen cases still remained undiagnosed.

Our study revealed that bone marrow examinations had the highest diagnostic yield for neoplastic disorders. This was similar to the study conducted by Manion et al on elderly patients in which specific diagnosis was achieved in 43% of total 79 cases, all of which were neoplastic disorders.[7] However, studies conducted on elderly patients by Sulakshana et al and Gulati et al showed specific diagnosis in 94% of total 50 cases and 83% of total 83 cases respectively which included both neoplastic and nonneoplastic disorders.[8,11]

In our study, neoplastic disorders constituted 32 cases (54%) and nonneoplastic disorders constituted 14 cases (23.7%) of the total 59 cases. Out of 32 neoplastic disorders, 31 cases (52.5%) were hematological malignancies and one case (1.7%) was metastatic carcinoma (figure1). In the study by Gulati et al on elderly patients above 60 years of age, neoplastic disorders were more common over non neoplastic disorders and constituted 37 out of the total 83 cases (44.5%). Nonneoplastic disorders constituted of 32 cases (38%).[11] Study conducted on all age groups by Mirzai et al and Kibria et alalso showed neoplastic disorder common over non neoplastic disorder-72.9% and 53.67% of cases respectively.[9,12]

In contrast, in the study conducted by Sulakshana et al on elderly patients above 60 years of age, nonneoplastic disorder was the most common disorder (60%) followed by neoplastic disorder (34%).[8]Nonneoplastic finding was more common in the studies on general patients by Bashawri et al, Gandapur et al and Ranabhat et al.[13,14,15]

In our study, the most common neoplastic disorder was acute leukemia (10 cases) followed by myeloproliferative neoplasm (eight cases), myelodysplastic syndrome (six cases) and multiple myeloma (five cases). AML constituted nine cases and ALL constituted only one case of acute leukemia. One case diagnosed as acute leukemia based on morphological findings on bone marrow aspiration turned out to be CML with a blast crisis followingfurther evaluation of flow cytometry, cytogenetic and clinical findings.Myeloproliferative neoplasm constituted three cases of CML, three cases of essential thrombocythemia and two cases of polycythemia vera. There was a single case each of CLPD and solitary plasmacytoma.

In the study conducted on elderly patients, Manion et al showed myelodysplastic syndrome as the commonest neoplastic disorder (32%) followed by myeloproliferative neoplasm (29%) and multiple myeloma (14.7%). Acute leukemia consisted of only three cases.[7] Study by Sulakshana et al showed multiple myeloma (12%) as the commonest neoplastic disorder followed by chronic lymphocytic leukemia (6%).[8] Gulati et al also showed multiple myeloma (18%) as the commonest neoplastic disorder followed by Non-Hodgkin lymphoma (14.8%) and acute and chronic leukemias (4.8%).[11]However in our studyacuteleukemiawas more common than multiple myeloma similar to the studies conducted by Ahmed et al, Kibria et al, Bashawri LA et al, Laishram S and Pudasaini S et al on general patient populations.[10,12,13,16,17]

In our study, the most common non neoplastic diagnosis was anemia due to renal failure (8.4%) followed by megaloblastic anemia (5.08%) and anemia of chronic inflammation (5.08%). Nutritional anemia followed by aplastic anemia were the most common non neoplastic disorders in the study conducted on elderly population by Sulakshana et al and Gulati et al as well as in the study conducted on all age groups by Ahmed et al and Kibria et al.[10,12] Megaloblastic anemia was also the commonest neoplastic disorder in the study conducted Bashir et al and Kakati et al on general patient population.[18,19]

Anemia of renal failure was more common than megaloblastic anemia in our study which was in contrast to other studies conducted on elderly populations and on general patient populations. The higher frequency of anemia of renal failure in our study could be due to the high degree of suspicion of plasma cell myeloma in elderly patients with renal failure for which bone marrow examination is frequently carried out.

Smaller sample size as well as the limited range of molecular tests and cytogenetic studies were the main limitations in our study. Undiagnosed cases in our study could have been due to the initial stage of underlying disorder with subtle changes on bone marrow morphology. These cases could have been diagnosed on follow up with subsequent bone

marrow examinations which was not done in our study.

CONCLUSION

The indications for bone marrow examination in elderly patients were similar to those in general patients, with bicytopenia /pancytopenia being the commonest followed by suspected plasma cell myeloma and acute leukemia. A high diagnostic yield of bone marrow examination was seen in this study, and it was higher for neoplastic disorders as compared to nonneoplastic conditions. The diagnostic yield increased further by correlating marrow findings with clinical parameters and ancillary tests. Despite all efforts in a small number of cases specific diagnosis was not achieved

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