

## Patterns of hematological and non-hematological malignancies in bone marrow in a tertiary care hospital in Nepal - 11 years study

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### ABSTRACT

Developing countries bear more than half of the global cancer burden and the leukemia comprises of 3% of all malignancies with an incidence of 300,500 per year. The patterns of subtypes of leukemias vary in different populations and geographic areas. Here, we analyze both the hematological and non-hematological malignancies in the Western region of Nepal. This is a retrospective study done from January 2000 to June 2011. All cases of bone marrow malignancies including leukemias, multiple myeloma and infiltration/metastasis to bone marrow were included in the study. Morphological subtypes {FAB (French, American and British) classification}, gender, age at diagnosis and peripheral blood counts of all the cases were analyzed. A total of 155 cases of hematological and non-hematological malignancies were reported during this period. Age ranged from 1 year to 82 years. Among 123 leukemia cases, acute myeloid leukemia (AML) was the commonest (80 cases) followed by chronic myeloid leukemia (CML) (20cases), acute lymphoid leukemia (ALL) (16 cases) and chronic lymphoid leukemia (CLL) (7 cases). The commonest childhood leukemia below 15 years was AML followed by ALL. The commonest subtypes of AML and ALL were M2 and L2 respectively. CML cases in our study were less common and females were more affected than other parts of the country. There were 23 cases of multiple myeloma and 9 cases of infiltration/metastasis to marrow. Males were more affected by multiple myeloma in our study. Our data reflects bone marrow malignancies in the Western region of Nepal which is more comparable to the Central than Eastern region of Nepal.

**Keywords:** Acute leukemia, bone marrow, chronic leukemia, childhood leukemia, multiple myeloma, metastasis.

### INTRODUCTION

Developing countries bear more than half of the global cancer burden because 75% of world populations live in these countries.<sup>1</sup> World wide leukemia constitute 3% of all malignancies and the incidence is 300,500 per year. It constitutes 3.6%, 4.6%, 3.5% and 2.5% of all the malignancies in South East Asia, Nepal, India and China respectively.<sup>2</sup> Leukemia was first identified as a malignancy in 1889.<sup>3,4</sup> Presently it can be defined as a clonal neoplasm of hematopoietic stem cells characterized by uncontrolled proliferation of immature cells in bone marrow and spilling into peripheral blood. The patterns of subtypes of leukemias in different populations and geographic areas are different.<sup>5,6</sup> Here we analyze the hematologic and non-hematologic malignancies reported in the bone marrow in the Department of Pathology, Manipal Teaching Hospital. In our knowledge, this is the first study of this kind performed in the Western region of Nepal.

### MATERIALS AND METHODS

The study has been carried out retrospectively in the Department of Pathology. A total of 982 cases of bone

marrow study (aspiration and biopsy) have been carried out during the period of January 2000 to June 2011. Among these, all cases of hematologic and non-hematologic malignancies reported on bone marrow, including leukemia, multiple myeloma and metastatic deposits have been retrieved and reviewed. The leukemia cases were reported according to FAB classification on the basis of morphological and cytochemical features with routine stain (Giemsa) and special stains e.g., Myeloperoxidase (MPO) and Periodic acid Schiff (PAS). In the diagnosis of myeloma, the diagnostic criteria of Kyle and Greipp were followed. Morphological subtypes, gender, age at diagnosis and peripheral blood counts were analyzed in all cases. Patients under 15 years of age were considered as "children" as in other literature.<sup>7</sup>

### RESULTS

There were a total of 155 malignant cases including hematopoietic and non hematopoietic entities. Table-1 shows the number, frequency, gender distribution and age distribution of all cases. Among a total of 123 leukemia cases, 96 cases were acute leukemia which included 80 cases of acute myeloid leukemia (AML)

**Table-1:** Distribution of all malignant cases reported on bone marrow

Entities	n.	(%)	Male	Female	Adult	Children (<15 yrs)
AML	80	52	41	39	65	15
ALL	16	10	10	6	6	10
CML	20	13	9	11	19	1
CLL	7	5	6	1	7	-
MM*	23	15	16	7	23	-
Mets + infiltr**	9	6	5	4	8	1
TOTAL	155		87	68	128	27

\*Multiple myeloma, \*\*metastasis and infiltration to marrow

and 16 cases of acute lymphoid leukemia (ALL). 27 cases were diagnosed as chronic leukemia, including 20 cases of chronic myeloid leukemia (CML) and 7 cases of chronic lymphoid leukemia (CLL). Males were affected more by leukemia, as a whole, than females in a ratio of 1.2:1. Over all, adults were affected more than children. In adults, the commonest leukemia was AML, followed by CML while among children the commonest type was AML followed by ALL.

The age of patients with AML ranged from 2 years to 82 years with a mean of 38 years. Among FAB subtypes of AML, the commonest was M2 (32 cases, 40%) followed by M1 (15 cases, 19%), M4 (13 cases, 16%), and M3 (12 cases, 15%) [Table-2]. AML affected males and females in equal ratio (1:1). Adults were affected by AML more than children in a ratio of 4.3:1. Among childhood AML (15 cases) M1 was the commonest subtype (5 cases) followed by M4 (4 cases), M2 and M3 (both 3 cases each) [Table 2, 5].

We reported a total 16 cases of ALL, 10 (62%) of which were in children [Table-3]. L2 was the commonest subtype in both adults and in children. All 3 cases of L1 were in children while the only case of L3 was in a female patient of 45 years of age.

**Table-3:** Distribution of ALL subtypes (FAB classification)

ALL Subtypes	n.	(%)	Male	Female	Adult	Children (<15 yrs)
L1	3	19	2	1	-	3
L2	12	75	8	4	5	7
L3	1	6	-	1	1	-
TOTAL	16		10	6	6	10

**Table-2:** Distribution of AML subtypes (FAB classification)

AML subtypes	n.	(%)	Male	Female	Adult	Children (<15 yrs)
Mo	2	3	2	-	2	-
M1	15	19	7	8	10	5
M2	33	41	13	20	30	3
M3	12	15	7	5	9	3
M4	13	16	8	5	9	4
M5	3	4	2	1	3	-
M6	1	1	1	-	1	-
M7	1	1	1	-	2	-
TOTAL	80		41	39	65	15

Table-4 shows the distribution of all 20 cases of CML. Sixteen cases (80 %) were in chronic phase, all with myeloblasts less than 5% .4 cases (20%) were in accelerated phase with 10 - 19% myeloblasts. We did not have any case of CML in blast crisis. The only case in children group was a patient at age 18 months reported as CML in accelerated phase. Excluding the childhood CML patient, age of adult CML cases (19 cases) ranged from 25 to 72 years with most cases (15/19 cases) seen in age above 50 years.

All the 7 cases of CLL were in adults (57 to 85 years) and affected mainly males (6:1). Other than leukemia, we came across patients with plasma cell dyscrasia including 23 cases of multiple myeloma (MM) [Table-1] and 2 cases of monoclonal gammopathy of undetermined significance (MGUS). The age range of MM patients was from 35 to 79 years and males were affected 2.2 times more commonly than females. We also reported 9 cases of metastatic infiltration to bone marrow. Among these, 5 cases were with infiltration by non hodgkins lymphoma (NHL), 3 cases of adenocarcinoma metastasis and 1 case of metastatic rhabdomyosarcoma in a 1 year old female child.

**Table-4:** Distribution of CML in different phases

CML Subtypes	n.	(%)	Male	Female	Adult	Children (<15 yrs)
Chronic Phase	16	80	8	8	16	-
Accelerated phase	4	20	1	3	3	1
Blast crisis	-	-	-	-	-	-
TOTAL	20		9	11	19	1

Table-5: Distribution of childhood malignancies

Entities		n.	Male	Female	<5 years	5 - <10 years	10 - <15 years
AML (n=15)	M1	5	3	2	-	3	2
	M2	3	2	1	2	1	-
	M3	3	2	1	-	-	3
	M4	4	1	3	1	2	1
ALL (n=10)	L1	3	2	1	1	1	
	L2	7	5	2	3	3	1
CML (n=1)	Acc Phase*	1	1	-	1	-	-
Mets** (n=1)	RMS ***	1	-	1	1	-	-

\*Accelerated phase, \*\*Metastasis, \*\*\*Rhabdomyosarcoma

On analysis of clinical features of acute leukemia patients, pyrexia was the commonest presenting symptoms followed by weakness, pallor, echymosis and bone pain. The CML patients presented with fever, fatigue and organomegaly. Majority of CLL were asymptomatic followed by lymphadenopathy. Multiple myeloma patients mostly presented with bone pain, fatigue and pathological fractures while some were asymptomatic and diagnosed incidentally.

Table-5 shows the distribution of all childhood malignancies and Table-6 shows the distribution of cases according to peripheral blood parameters which are further discussed below.

## DISCUSSION

**Acute Myeloid Leukemia:** Acute leukemia has a world wide incidence of 4/100000 per year, 70% of which is

AML.<sup>4</sup> AML is a clonal expansion of myeloid blasts in bone marrow, blood or other tissues.<sup>4</sup> FAB classification is based on morphological and cytochemical properties of the blasts assessed by routine Leishman or Giemsa and special stains e.g. MPO and Sudan Black B (SBB). In our study, AML (n=80) comprised 83% of acute leukemia cases (n=96) and 65% of all leukemia cases (n=123). In contrast, Bhutani *et al*<sup>8</sup> mentioned that in different studies in India the frequency of AML varied from 13% to 38% of all leukemia cases. In studies in Nepal, by Kulshrestha *et al* in the Eastern region<sup>3</sup> and Hamal in the Central region,<sup>9</sup> AML comprised 29% and 33% of all leukemia respectively. In the Central region,<sup>9</sup> the commonest leukemia was AML similar to as in our study (Western region) but in much less percentage. In the Eastern region, the commonest leukemia was CML.<sup>3</sup> In AML subtypes, the commonest subtype was M2 (33/80, 41%) as in the Eastern region (30/95, 54%).

Table-6: Peripheral blood findings in all hematological malignancies cases in the study

	Hb ( gm/dl)		WBC ( per mm <sup>3</sup> )			Platelet ( per mm <sup>3</sup> )	
	<10	>10	<4000	4000-11000	>11000	< 10 <sup>5</sup>	>10 <sup>5</sup>
AML (n=80)	69	11	24	24	32	65	15
ALL (n=16)	12	4	1	5	10	16	-
CML (n=20)	12	8	-	-	20	6	14
CLL (n=07)	5	2	-	1	6	3	4
MM (n=23)	12	11	05	15	3	5	18

Other large series on AML from UK,<sup>10</sup> USA,<sup>11</sup> Pakistan,<sup>12</sup> Libya<sup>13</sup> found M2 as the commonest subtype (25%, 29%, 32%, 57% respectively) while other studies from Saudi Arab<sup>14,15</sup> and Pakistan<sup>16,17</sup> found M4 as the commonest subtype (58%, 40%, 37%, 46% respectively).

AML is a disease of older population with the median age being 60 to 65 years in different studies.<sup>4,8</sup> In our study, the mean age was 38 years. Some studies in India found the median age 30 years.<sup>8,18,19</sup> Studies in Pakistan and Saudi Arab also showed a mean age in thirties which is lower than Western countries.<sup>12,15,16,17</sup> We reported 1 case of M4Eo, 1 case of M5a, and 2 cases of M5b. We had only 1 case of AML M7 which showed marked grade 3 reticulin fibrosis in biopsy as the association of M7 and fibrosis is well documented.<sup>20</sup>

AML patients (n=80) showed a wide variation in Hb, total leucocyte count (TLC) and platelets. 69 patients had anemia (Hb<10gm/dl) and 65 patients had low platelets (<10<sup>5</sup>/cmm). Interestingly, 48 patients (60%, 48/80) had normal or low TLC with presence of peripheral blasts. Low TLC with a relative low percentage of peripheral or bone marrow blasts may present diagnostic difficulties.<sup>7</sup>

**Acute Lymphoid Leukemia:** ALL can be identified morphologically and with PAS stain block positivity and can be further classified into L1, L2 and L3 based on "ALL score".<sup>7,21</sup> ALL comprises 30% of childhood cancers worldwide and 75% cases occur in below 10 years and 50% occur below 5 years of age.<sup>22</sup> In our study, we reported 16 cases of ALL comprising 17% of acute leukemia (16/96) cases and 13% of all leukemia cases (16/123). The frequencies of ALL in Eastern and Central Nepal were 20% and 26%.<sup>3,9</sup> In India, the rates ranged from 9% - 39% in different series with a higher incidence in Southern India.<sup>8</sup> In one study by Al-Bahar *et al* from Kuwait, ALL was the commonest (44%) of all types of leukemia.<sup>23</sup> In our study, of total 16 ALL cases, 10 cases (63%) were below 15 years, 4 cases (25%) below 10 years and 4 cases (25%) below 5 years. In the international literature, ALL-L1 is the commonest subtype in children and L2 in adult.<sup>7,24</sup> However in our study ALL-L2 is the commonest type in both adults and children below 15 years. Among ALL (n=16), 12 patients had anemia (Hb<10gm/dl) and all had low platelets (<10<sup>5</sup>/cmm). 10 cases (63%) of ALL had high TLC more than 11000/mm<sup>3</sup> while 1 case had TLC less than 4000/mm<sup>3</sup>.

**Leukemia in children:** Though majority of leukemia occur in older people, it is the commonest malignancy in children and adolescents.<sup>25</sup> Among a total of 123 leukemia cases, we had 26 cases (26/123, 21%) of childhood leukemia. The frequency of childhood

leukemia is comparable to studies in India (64/242, 26.5%) and Eastern Nepal (48/196, 24%).<sup>3,26</sup> Male to female ratio was 1.6:1 compared to 3.2:1 in the study by D'Costa *et al* in India.<sup>26</sup>

In childhood leukemias, 73% is ALL which peaks at age 2-4 years of age.<sup>25,27</sup> In United States, majority of new ALL cases are younger than 15 years old.<sup>22</sup> In our study, the commonest leukemia below the age of 15 years was AML (15 cases) followed by ALL (10 cases) [Table 5]. 8 of 10 cases of ALL were in less than 10 years of age. Males are known to be affected more than female in a ratio of 1.3:1 which in our study was 2.3:1.<sup>22</sup> In contemporary international literature and in the Eastern Nepal, ALL L1 subtype is more common in children.<sup>3,24</sup> However, we found more ALL L2 subtype (7 cases) than L1 (3 cases) in children.

AML, according to international data, comprises of 15 to 20% of total childhood leukemias with the highest rates among infants below 1 year.<sup>5</sup> In the current study, 58% of childhood leukemia (26 cases) were AML (n=15). The commonest subtype was M1 (5 cases) followed by M4 (4 cases), M2 and M3 (3 cases each). Male and female were almost equally affected as seen in adults.

Analyzing our data [Table-5], we noted that in the age group below 10 years, AML and ALL cases are almost equal (9 and 8 cases respectively) but in the age group 10-15 years AML is more common than ALL (6 and 2 cases respectively). Though in our study, AML is the commonest childhood leukemia below 15 years, the difference between AML and ALL is less in the age group less than 10 years and in the age group less than 5 years, ALL is found more than AML [Table-5].

**Chronic Myeloid Leukemia:** World wide CML accounts for 20% of all cases in leukemia.<sup>28</sup> We reported 20 cases comprising of 16% (20/123) of all leukemias which is less than Eastern (35%) and the Central (30%) Nepal.<sup>3,9</sup> In the Central region, CML was the commonest type of leukemia.<sup>3</sup> Different studies in India show frequency of CML ranging from 30 to 56%, being the commonest form of malignancy in adults.<sup>29-31</sup> CML shows slight male predominance.<sup>32,33</sup> In our study, there was slight female predominance in contrast to data of Eastern region of Nepal (M:F=2.5:1).<sup>3</sup> As expected, 80% (16/20) of CML were in chronic phase. All patients with CML had high WBC and majority had anemia and high platelets. One case had TLC more than 2x10<sup>5</sup>/mm<sup>3</sup>, 4 cases had between 1x10<sup>5</sup>/mm<sup>3</sup> and 2x10<sup>5</sup>/mm<sup>3</sup>. One case of CML was reported in a male child of 18 months of age which was in accelerated phase.

**Chronic Lymphoid Leukemia:** In the Western countries, CLL is the most common type of adult leukemias which

virtually rarely occurs before 50 years.<sup>5,34</sup> However it is infrequent in Asian countries.<sup>8</sup> In our study, CLL is the least common leukemia comprising 6% of all leukemia cases (7/123), similar to studies in Nepal and India.<sup>3,8,9</sup> The youngest patient was 57 years. Males are 6 times more affected in our study in contrast to international data with male to female ratio 2:1.<sup>34,35</sup> Six cases had high TLC and 1 case had TLC less than 11000/mm<sup>3</sup> (but more than 10000/mm<sup>3</sup>) [Table-6].

**Multiple Myeloma:** Multiple myeloma represents 15% of all hematological malignancies which is similar to our data.<sup>36</sup> Males are known to be affected equally as females in other literatures,<sup>37</sup> though in the current study males were affected more than twice as common as females (2.2:1). Median age is known to be 71 years.<sup>38</sup> In our series, the age range was from 42 to 72 years with a mean age of 63 years. In our series 52% of MM patients presented with anemia and majority had normal TLC and platelet count. We had 2 cases of MGUS of age 70 years and 62 years which were followed up for a period of 1 year, during which no new symptoms developed. Subsequently, they were lost to follow up.

**Metastasis and Infiltration:** The bone marrow is one of the more common organs to be involved by tumors that metastasize via blood stream.<sup>39</sup> We reported 5 cases of marrow infiltration by non-Hodgkin's lymphoma which were previously diagnosed on lymph node biopsy. In adults, the nonhematogenous tumors most often seen marrow are carcinomas of prostate, breast and lung.<sup>40,41</sup> We had 3 adult cases with adenocarcinoma deposits to marrow with male to female ratio 2:1. In these adenocarcinoma cases, 1 case was of prostatic adenocarcinoma, 1 case was undifferentiated and the other (female) case was of unknown primary (lost to follow up). In childhood, small-round-cell tumors are a group of malignancies including neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma and acute lymphoblastic leukaemia/lymphoma.<sup>42</sup> All of these malignancies show a propensity to metastasize to bone marrow and account for the majority of marrow metastasis in children.<sup>42,43</sup> The only case of childhood metastasis in the current series was seen in a known case of 1 year old female infant with rhabdomyosarcoma. Rhabdomyosarcoma manifesting as a systemic disease is very rare and cases showing diffuse metastasis in the bone marrow are most unusual.<sup>44</sup> They may present mimicking acute leukemia and may pose difficulties in diagnosis.<sup>44</sup>

The pattern of age and geographic distribution of leukemia vary widely in different countries. Our data reflects the distribution of hematological and non-hematological malignancies in marrow in the western part of the country. AML was the commonest leukemia in both adults and children below 15 years. CLL was the

least common type of leukemia. In ALL the commonest type was L2. Most of CML, all CLL and all MM were seen in adults. In CML, more females and in MM more males were affected than contemporary literatures.

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