

Documentation of Myeloproliferative Disorder as the Commonest Hematological Malignancy in Predominant Rural Based Pilot Study at Punjab (India): An Incidental Finding or Association

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ABSTRACT

Background: Pilot studies (standard scientific tool) are helpful for researchers in conducting preliminary analysis before committing resources for a main study to follow. The present pilot study was undertaken in the northern part of India so as to take a glimpse of the pattern of hematological malignancies in an area which is mostly based on the agricultural economy and the hazards associated with it. These demographic based studies are often helpful in defining the burden and to ascertain the trends of the disease in the selected population.

Method: A 3 year retrospective study was conducted in the hematopathology unit of the Department of Pathology, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab (India) from a period of January 2012 to December 2014. Data regarding demographic/epidemiological details including clinical presentation, indication for the procedure was noted. Only the cases of hematological malignancies were included in the study. The results thus obtained were recorded and analyzed by descriptive statistics.

Results: Of 1840 cases, 147 (7.98%) were hematological malignancies with Male to Female ratio being 2:1. After retrieving the residential records, it was noted that most of the patients were natives of Punjab state. The most common peripheral blood finding in hematological malignancies cases were pancytopenia (38.09%), followed by bicytopenia (27.2%). According to the clinical presentation most common presentation recorded was hepatomegaly (42.1%), followed by splenomegaly (28.57%). The commonest hematological malignancy in our study was MPD (Chronic Myeloid Leukaemia primarily) followed by Lympho-proliferative disorders (which included Chronic Lymphocytic Leukaemia, Non Hodgkin's Lymphoma and Hairy Cell Leukaemia). Combining both the categories, the so called chronic leukaemias contributed almost 2/3 of cases (72.78%).

Conclusions: In contrast to most of the reported institutional based cases from India and the neighboring countries (including many developing countries of Asia) which have recorded acute leukaemia (ALL/AML) overall as the most common hematological malignancy; the higher incidence of chronic leukaemias in our study is interesting.

The finding of CML as more common of the chronic leukaemias in comparison to the CLL and other LPD's is noteworthy. This trend needs to be watched carefully and a further study is planned to monitor the overall outcome over the next few years.

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Introduction

Hematological disorders manifest in many ways. A patient may be asymptomatic as in compensated anemia or may be suffering with a life threatening emergency as in a hematological malignancy (HM) per se or due to the complication of its therapy (tumor lysis syndrome). Apart from the clinical history, routine hematological investigations, ancillary investigations (such as electrophoresis and other special tests), including cytochemistry and radiological investigations; Bone marrow examination (bone marrow aspiration and biopsy) are considered essential and are corner stone of management of hematological disorders.^[1] Although in cases of HM; flowcytometry is often considered gold standard in reaching a diagnosis, the importance of a minimal invasive and a outpatient procedure to reach an initial diagnosis cannot be overstated especially in third world and resource challenged countries where such facilities and other molecular studies are out of reach for much of the population. In most instances bone marrow examination is the most definitive method of differentiating hematological malignancies from non- malignant hematological disorders.

The underlying cause of most HMs remains unaccountable. Many factors such as infectious agents, autoimmunity, drugs, inherited disorders and environmental agents have been implicated.^[2]

The present study was essentially a pilot study which was undertaken over a period of three years in a single tertiary care centre in the northern part of India so as to take a glimpse of the pattern of HM in an area which is mostly based on the agricultural economy and the hazards associated with it. A comparison was also drawn with areas in and around Indian subcontinent and rest of the industrialized world. These demographic based studies are helpful in defining the burden and to ascertain the trends of the disease in the selected population. This in many instances imparts valuable knowledge and information to plan and implement various health programmes and correctional measures to limit the disease burden.

Objectives of This Study are

1) To find out the demographic spectrum of HMs according to age and sex 2) To correlate between the PBF findings ,clinical presentations and bone marrow aspiration and biopsy findings, and 3) To sub-type the individual HMs for ascertaining the pattern.

Materials & Methods

A 3 year retrospective study was conducted in the Department of Pathology, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab (India)

from a period of January 2012 to December 2014 catering to majorly rural and urban dwellers as well. The study was approved by research ethics committee of the institute. In total 1840 cases were studied by retrieving the records from the departmental archives. Detailed information regarding age, sex, clinical presentation, indication for the procedure was noted. Data was collected and subsequently analyzed .The findings on aspirate and biopsy were compared to each other. The standard technique was employed for obtaining the aspirate samples using the Salah's needle from posterior superior iliac spine. The trephine biopsy was performed using Jamshidi needle with the length of the biopsy core ranging from 1 to 3 cm. The biopsy was then fixed for minimum of 24 hours in 10% buffered formalin and then decalcified overnight in mixture of 8 % hydrochloric acid and 10 % formic acid in equal amounts. The fixation of the biopsy core was followed by automated tissue processing, paraffin embedding and sectioning. All the aspirate smears were routinely stained by May Grunwald Giemsa (MGG) while the trephine biopsy sections were stained by routine Hematoxylin and Eosin (H&E) stain. The demographic variables were sex and age grouping. The research variable was pattern of the disorder on bone marrow aspirate examination.

All the cases of non malignant hematological disorders (nutritional etc.) and myelodysplasia were excluded from the study. Only the cases of hematological malignancies (HM) were included in the study. In all the cases informed and written consents were obtained. The clinical details as well as the slides were reviewed again by trained hematopathologists. The results thus obtained were recorded and analyzed by the means of descriptive statistics.

Results

Of 1840 cases, 1693 (92.01%) were non-malignant hematological disorder (TABLE 1) and 147 (7.98%) were hematological malignancies with Male to Female ratio being 2:1. After retrieving the residential records, it was noted that most of the patients were natives of Punjab state.

The most common peripheral blood finding in hematological malignancies cases were pancytopenia (38.09 %), followed by bicytopenia (27.2 %), anemia (16.32%), thrombocytopenia (15.64%) and normocytic normochromic picture (4.08%) respectively (TABLE 2).

According to the clinical presentation most common presentation recorded was hepatomegaly (42.1%), followed by splenomegaly (28.57%), lymphadenopathy (18.36) and pallor (10.88%) (TABLE 3). For malignancies most common age group involved was

60 years and above (63 cases; 42.8 %) (TABLE 4). Hematological malignancies cases comprised of myeloproliferative disorders (MPD) comprising of 69 cases (46.9 %) followed by lympho-proliferative disorder

(LPD) comprising of total 38 cases (25.8%) followed by acute leukaemias total 24 cases (16.32 %) , plasma cell dyscrasia total 9 cases (6.1 %) and bone marrow infiltrative disorder total 7 cases (4.7 %) respectively (TABLE 5).

Table 1: Distribution of malignant vs non-malignant hematological disorders in bone marrow.

YEAR	NON -MALIGNANT	MALIGNANT	TOTAL
2014	671	74	743
2013	493	32	525
2012	531	41	572
	1695	147	1840
PERCENTAGE	92.02	7.9	

Table 2: Various PBF findings in hematological malignancies.

PRESENTATION	2014	2013	2012
PANCYTOPENIA	30	12	14
BICYTOPENIA	20	08	12
ANEMIA	10	06	08
THROMBOCYTOPENIA	10	05	08
NORMAL	04	00	02

Table 3: Various clinical presentation in hematological malignancies.

CAUSES	2014	2013	2012	TOTAL
HEPATOMEGALY	35	12	15	62
SPLENOMEGALY	21	10	11	42
LYMPHADENOPATHY	10	07	10	27
GENERALIZED WEAKNESS	08	03	05	16

Table 4: Distribution of hematological malignancies according to various age groups.

YEAR	0-15	15-40	40-60	MORE THAN 60
2014	04	13	27	30
2013	02	06	09	15
2012	03	08	12	18
TOTAL	09	27	48	63
PERCENTAGE	6.1	18.3	32.6	42.8

Table 5: Subtyping of various hematological malignancies detected.

YEAR	ACUTE LEUKEMIA	LYMPHO PROLIFERATIVE DISORDERS	MYELOPROLIFERATIVE DISORDER	PLASMA CELL DYS-CARIASIS	BONE MARROW INFILTRATION
2014	11	19	29	7	04
2013	04	10	17	01	01
2012	09	09	23	01	02
TOTAL	24	38	69	9	7
PERCENTAGE	16.32	25.8	46.9	6.1	4.7

Discussion

It is well documented that developing countries bear upto 50 % of all the global cancer burden and of these HMs constitute 3 % of all malignancies with an incidence rates of 300,500 per year.^[3] According to data published by IARC regarding incidence of HMs; it is 3.6 %, 4.6%, 3.5%

and 2.5% of all the malignancies in south-east Asia, Nepal, India and China. However; individual centre based studies yield important information as they can be used to compare the rates calculated from the local area not only with the individual country average but also with different parts of the country and internationally as well. In the present pilot

study we tried to analyze the data obtained from the patients reporting to our institute to know the relative frequency of different hematological disorders with emphasis mainly on the spectrum of hematological malignancies.

Employing this principle we found that in our institute HMs constituted 7.98% in our study which was much lower than the other institute based (local) reported series in and around India such as 18 % reported by Tahlan et al ^[4], 27.12% by Rahman et al ^[5], and 47.48% by Al-Ghazaly J et al. ^[6]

Organomegaly constituting hepato splenomegaly (70.74%) was the commonest clinical presentation noted in our study unlike pallor and lymphadenopathy noted in other studies. Rate of splenomegaly in many studies has been documented around 40 % of all the splenomegaly patients and around 50% in many patients of HM especially the ones suffering from CML.^[7, 8]

Male preponderance was seen across almost all of the lesions in our study except in multiple myeloma and Hodgkin's disease. However; in many studies around the world LPD- (Chronic Lymphocytic leukemia and Non Hodgkin's lymphoma) are more common in female population.^[9, 10] The finding of male preponderance in this part of the world maybe due to more assertiveness of the males to seek healthcare and neglect by the females over

healthcare which is a prevalent behavior throughout the resource challenged countries.

Peripheral blood film (PBF) is a basic and a highly informative hematological tool at the clinician's disposal in screening, diagnosis and monitoring of disease progression and therapeutic response. The most common PBF finding in hematological malignancies cases in our study in decreasing order was pancytopenia, bicytopenia, anemia, thrombocytopenia and normocytic normochromic picture. The findings almost concur with work done by other researchers who have also noted cytopenias as the most common presentation in hematological malignancies with bicytopenia being the most common.^[9, 11] Most of our patients were of pancytopenia with bicytopenia being the second most common presentation on PBF. Hence, presence of pancytopenia or bicytopenia in a PBF should be very carefully assessed by the reviewing hematologist.

In our study, we observed MPDs accounting for upto half the cases of all hematological malignancies (46.9 %). Most of these cases were of chronic myeloid leukemia (CML) - chronic phase with very few cases of accelerated phase and the blast crisis [Figure 1a & 1b]. The second most prevalent hematological malignancy was LPD (25.8%) [Figure 2a & 2b] followed by acute leukaemias (16.32 %) [Figure 3a & 3b], plasma cell dyscrasia (6.1 %) [Figure 4a & 4b] and bone marrow infiltrative disorders 7 (4.7 %) respectively.

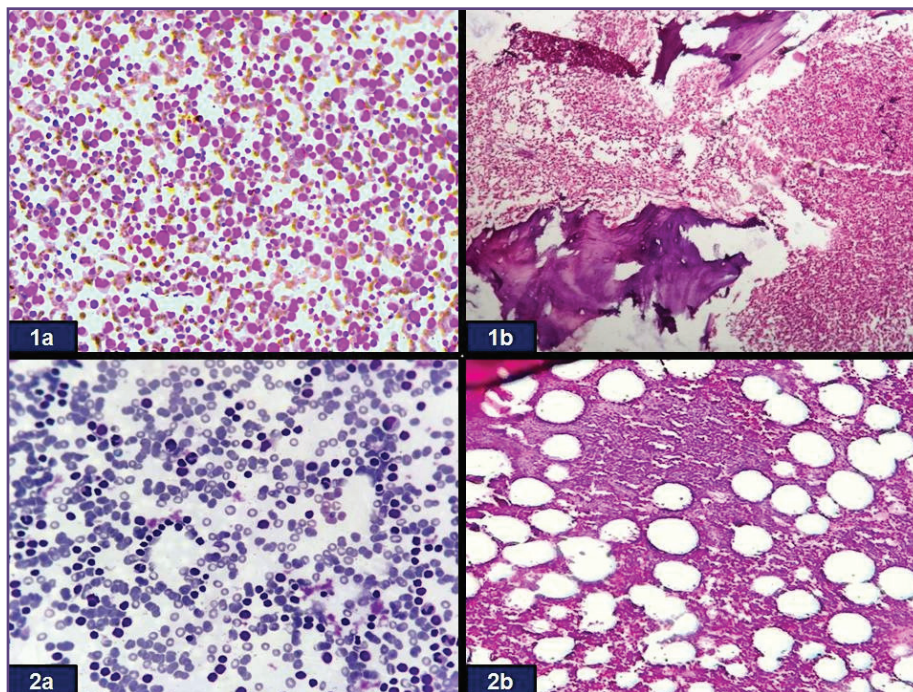


Fig. 1a: Bone marrow aspiration smear of CML showing myelocytes, meta myelocytes and band forms (MGG, x 10) with corresponding tissue section in Figure 1b (H&E, x 10). **Figure 2a :** CLL bone marrow aspiration revealing mainly mature lymphocytes (MGG, x 10) with diffuse pattern of infiltration on bone marrow biopsy in Figure 2b (H&E, x 10).

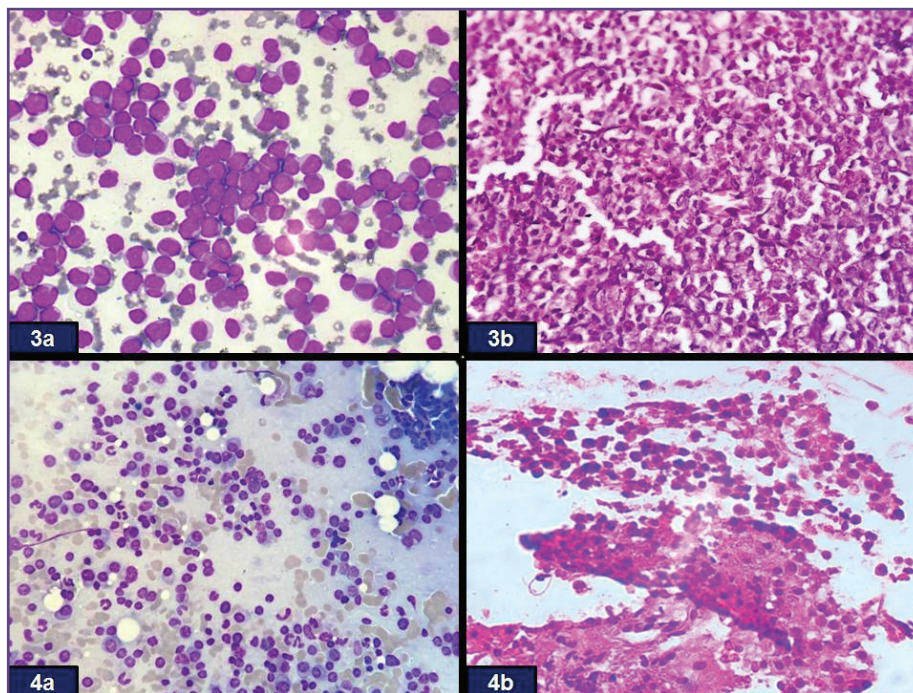


Fig. 3a: Bone marrow aspiration smear showing cellular infiltration of blasts in a case of acute leukaemia (MGG, x 20) with corresponding tissue section in Figure 3b (H&E, x 10). **Figure 4a :** Increased number of plasma cells in a case of multiple myeloma on bone marrow aspiration (MGG, x 10) with corresponding tissue section in Figure 4b (H&E, x 10).

It is interesting to note that while in most of the reported institutional based cases from India and the neighboring countries of Nepal, Bangladesh, Pakistan including many developing countries of Asia have recorded acute leukaemia (ALL/AML) overall as the most common hematological malignancy recorded followed by lymphomas. According to the published research, Pudasaini S et al^[12] and Rahim et al^[4] have reported acute leukaemia to be 12.3% and 24.28 % respectively with some researchers such as Al –Ghazy^[5] and Tahlan et al^[3] reporting them to be as high as 41 % and 37.31 % respectively.

In contrast the commonest HM in our study was MPD (CML primarily) followed by LPD (which included CLL, NHL and HCL). Combining both the categories, the so called chronic leukaemias contributed almost 2/3 of cases (72.78%). In most of the studies described above of the Asian population the LPD/NHLs were the second most common HMs after leukemia.^[3, 5, 11, 13]

The finding of number of chronic leukaemias being more than that of acute leukaemias is in line with observations that had been made in various studies of African and industrialized western world where there is a definite preponderance of the chronic leukaemia.^[14, 15, 16, 17] Similarly morphologically when chronic leukaemia were segregated; the myeloid was found to be more common

in this study that lymphatic leukaemia. This also is in line with the reports from the western hemisphere and some African studies.

In fact the high prevalence of chronic leukaemias especially CML noted in this study agrees with observations from published studies from Africa and the USA, where LPD's are the most common HM followed by CML.^[17, 18, 19]

CML as the most frequent HM in this study, accounting for 43.53% of the hematological malignancies reviewed are comparatively higher and unique finding compared with the figures from other studies. A possible reason for the lower number of cases encountered for the acute leukaemias in our study may be due to the fact that not many pediatric patients were included in the study and also it may also point towards an unfortunate fact of higher child mortality rate in our country where many basic facilities for diagnosis and treatment are often out of reach and the presence of a world class apex centre in the form of Post Graduate Institute of Medical Education and Research at Chandigarh which is in vicinity of our institute. Several other factors may also be contributory to the above finding as it is documented that the mean survival of acute leukaemic patients is low in developing countries due to late presentation in hospital, unavailability of required chemotherapeutic drugs either due to poor financial status of the patients, or due to

difficulty in procuring the drugs.^[20, 21] This unfortunate trend is well documented in the minority sub-populations of African Americans and Hispanics also in comparison to white Caucasians.^[22]

The higher incidence of chronic leukaemias in our study correlating with western hemisphere may also have an interesting hypothesis as the habits (food and social) and also the overall human development index (HDI) and average per capita income in this area of India is comparable to many of the middle income economies. The dietary habit and the environmental risk factors are almost now similar to the population of the western hemisphere. The longevity of the Punjabi population (higher life expectancy rates) and the patients of CML responding to the novel treatment of imatinib mesylate leading to improved 5 year survival rates can also have a bearing on the final results.

The finding of CML as more common of the chronic leukaemias in comparison to the CLL and other LPD's is noteworthy. This trend needs to be watched carefully and a further study is planned to monitor the trend over the next few years. Much of the occupation in Punjab (India) is agricultural based and the wide spread use of insecticide and pesticide as contaminant in soil and ground water of Punjabi population leading to malignancies is well documented. If this has a role in evolution of CML in Punjabi adult population at risk needs to be investigated as a recent study has corroborated increased risk of myeloid leukaemia with manufacturing and application of pesticides.^[23]

Conclusion

Pilot studies are standard scientific tools allowing researchers to do a preliminary analysis before committing resources and man power to serious research. The present pilot study highlights the recognition of MPD as the commonest HM in Punjabi population of north India. Although a single centre experience but this adds to information and can comment upon the current scenario and trends of HM in hitherto unstudied population. On basis of these findings further studies are being planned in collaboration with other state sponsored and non state sponsored institutes in this belt to calculate and corroborate the findings of the study with the risk factor of pesticide concentration with sub-type of leukaemias and the with different population sub-groups.

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Competing Interests

None

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