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BONE MARROW BIOPSIES IN PAEDIATRIC AGE GROUP AND THEIR CLINICOHAEMATOLOGICAL CORRELATION – A STUDY FROM WESTERN INDIA

Pathology

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ABSTRACT

Bone marrow aspirate and bone marrow biopsy are important procedures to diagnose various haematological and non-haematological diseases in children. Our aim was to study the spectrum of various haematological and non-haematological diseases which are diagnosed on bone marrow (BM) biopsy in children in a tertiary health care centre in India and to correlate these findings with the clinical presentation and haematological parameters of the patient. The slides of these biopsies were retrieved from the departmental archives and re-examined. The clinical details and haematological investigations of the patient were obtained from the medical records. Special stains and immunohistochemistry were studied wherever available. Overall, the mean age of the patients was 8.8 years and maximum patients were in the age group of 1-5 years. Male to female ratio was 1.56 and the commonest symptom and sign was fever and pallor respectively. The most common indication was cytopaenias. The various disorders diagnosed on bone marrow examination in our study was Acute leukaemia (28%), Aplastic anaemia (20%), Erythroid hyperplasia (15%), ITP (14%), Storage disorders (11%), Normal marrow (5%), Hypersplenism (2%), RVD related changes (1%), MDS (1%), Myelofibrosis (1%), Granulomatous reaction (1%). Among the 14 dry taps, the maximum number of cases were of acute leukaemia (50%). Our study highlights the wide spectrum of these disease entities in paediatric age group, for which bone marrow examination is an indispensable diagnostic tool.

KEYWORDS

Bone marrow examination, Bone marrow biopsy, paediatric age group, acute leukaemia, dry tap.

INTRODUCTION:

Bone marrow (BM) aspirate and BM biopsy are important procedures to diagnose various haematological and non-haematological diseases in children. While BM aspirate helps in cytomorphological evaluation of the haematopoietic cells, BM biopsy allows complete assessment of marrow architecture and the pattern of distribution of any abnormal infiltrate and the detection of focal bone marrow lesion [1]. Haematological disorders are quite frequent in paediatric population, ranging from iron deficiency anaemias to rare congenital disorders like Fanconi's anaemia [2]. The non-haematological conditions diagnosed on bone marrow include storage disorders, haemophagocytosis, etc [3]. Bone marrow examination provides diagnostically important information in these conditions. It helps in staging of neoplasms (lymphoma, neuroblastoma, etc.) and to monitor the recovery in patients undergoing bone marrow transplantation or marrow ablative chemotherapy.

AIMS AND OBJECTIVES:

- To study the spectrum of haematological and non-haematological diseases in children which are diagnosed on BM biopsy in a tertiary health care centre in India.
- To correlate the BM biopsy findings with the clinical presentation and various haematological parameters of the patient.

MATERIALS AND METHODS:

This is a retrospective observational study of 100 BM biopsies of patients ≤18 years of age received in the Pathology department of a tertiary health care centre in western India over a period of 4 years (2015 – 2018). The biopsies which were received for post treatment follow up were excluded. The clinical details and haematological investigations of the patient (complete blood counts, peripheral blood smear findings) were obtained from the medical records. The biopsy slides, which were processed as per the Hammersmith protocol [3], were retrieved from departmental archives and re-examined. The findings of Giemsa-stained BM aspirates and imprints were correlated with the biopsy findings. Other special stains and immunohistochemistry were studied wherever available. The results of the BM biopsies were analysed, and descriptive statistics were noted.

The parameters evaluated in a BM biopsy included overall cellularity; number and morphology of the cells of myeloid, erythroid, megakaryocytic lineages; presence of fibrosis; and other cells and lesions if any.

RESULTS:

Out of the total 405 biopsies received in our department over a period of 4 years, 100 biopsies belonged to paediatric patients (≤18 years of age). Overall, the mean age of the patients was 8.8 years and maximum patients were in the age group of 1-5 years. Male preponderance was seen and the commonest symptom and sign was fever and pallor respectively.

The various findings of the study are described in table 1, 2, 3, 4.

Table 1: The spectrum of disorders diagnosed on bone marrow examination in our study.

Diagnosis	Number
Acute leukemia	28
Aplastic anemia	20
Erythroid hyperplasia	15
Peripheral destruction of platelets	14
Storage disorders	11
Normal marrow	5
Hypersplenism	2
Changes related to RVD	2
MDS	1
Myelofibrosis	1
Granulomatous reaction	1
	100

Table 2: The age and sex distribution, most common clinical presentations of the patients and the cellularity of bone marrow biopsy for different disorders diagnosed in the study.

Diagnosis	Most common age group (years)	Sex	Most common symptom	Most common sign	Cellularity
Acute leukemia					
-ALL	1-5 (35%)	Male (80%)	Fever (95%)	Hepatosplenomegaly (85.7%)	Hypercellular (100%)
-AML	6-10 & 16-18 (37.5%)	Male (87.5%)	Fever (75%)	Pallor (62.5%)	Hypercellular (100%)
Aplastic anemia	11-15 (35%)	Male (70%)	Bleeding manifestations (80%)	Pallor (60%)	Hypocellular (100%)

Erythroid hyperplasia	1-5 (40%)	Male (60%)	Fever (47%)	Pallor (47%)	Normo and hypercellular (42.8%)
Peripheral destruction of platelets	11-15 (42.8)	Male (57.1%)	Bleeding manifestations(85.7%)	Petechiae/ecchymosis (57.1%)	Normocellular (50%)
Storage disorders	1-2 (63.6%)	Female (63.6%)	Abdominal distension (72.7%)	Hepatosplenomegaly (91%)	Normocellular (100%)

Table 3: The clinical indications for which bone marrow examination was performed and their frequencies.

Indications	Number
Cytopenias	51
HL malignancy	25
Storage disorder	15
Fever	6
Pallor with hepatosplenomegaly	2
Hemolytic anemia	1
	100

Table 4: The correlation of the final diagnoses given for the various indications described in table 3.

Indication	Diagnosis	Number
Cytopenias	Aplastic marrow	19
	Peripheral destruction of platelets	14
	Erythroid hyperplasia	9
	Acute leukemia	2
	c/w hypersplenism	2
	Normal marrow	2
	MDS	1
	Changes related to RVD	1
	Reactive marrow	1
HL malignancy	Acute leukemia	25
	Erythroid hyperplasia	1
Storage disorder	Storage disorder	11
	Normal marrow	3
	Erythroid hyperplasia	2
Fever	Acute leukemia	1
	Aplastic marrow	1
	Granulomatous inflammation	1
	Changes related to RVD	1
Pallor with hepatosplenomegaly	Erythroid hyperplasia	1
	Myelofibrosis	1
Hemolytic anemia	Erythroid hyperplasia	1

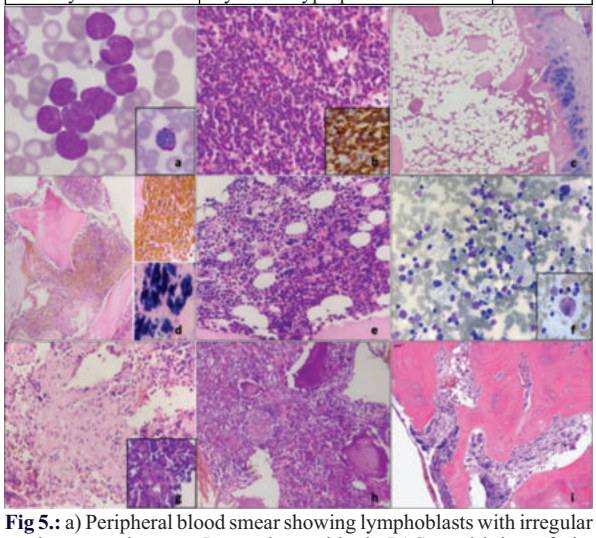

Fig 5.: a) Peripheral blood smear showing lymphoblasts with irregular nuclear membranes. Inset shows block PAS positivity of the lymphoblasts. (×1000); b) BM biopsy showing marrow packed with blast cells in a case of ALL (H&E ×400). Inset showing CD20 positivity of the blast cells (×400); c) BM biopsy showing markedly reduced cellularity and increased fat spaces in a case of aplastic anaemia (H&E ×100); d) BM biopsy in a case of thalassaemia major showing erythroid hyperplasia with sheets of haemosiderophages (H&E ×100, 400), inset showing Prussian blue positivity (×400); e) BM biopsy showing an increase in the number of megakaryocytes with mild erythroid hyperplasia in a case of peripheral destruction of platelets (H&E ×400); f) BM aspirate in a case of Niemann-Pick disease showing foamy macrophages (a: Giemsa ×400), inset showing oil red O positivity (×1000); g) BM biopsy showing sheets of Gaucher cells with crumpled paper/ fibrillary appearance of cytoplasm (H&E ×400). Inset - Gaucher cells showing PAS positivity (×400); h) BM biopsy showing presence of a granuloma (H&E ×100); i) BM biopsy showing widening of the osteoid seams and presence of fibrosis in a case of myelofibrosis secondary to rickets (H&E ×400).

The commonest diagnosis on bone marrow examination was acute leukaemia (28%). Of the 28 cases of acute leukaemia, 20 cases were found to be of acute lymphoblastic leukaemia (ALL), and 8 cases were of acute myeloid leukaemia (AML). Of the 20 cases of ALL, 9 patients showed high total leukocyte count (TLC), 5 patients presented with normal TLC, while 6 patients had a low TLC and no blasts in the peripheral smear. 65% of the cases of ALL showed reticulin fibrosis higher than grade 2. Eight cases were diagnosed as AML. A case of AML in Down's syndrome was diagnosed in a 15-month-old male child. Of the cases of AML, 5 cases had an increased TLC with presence of blasts in the peripheral smear and 3 cases showed a low to normal TLC. All the biopsies showed a marked increase in cellularity. Two cases of AML showed reticulin fibrosis higher than grade 2.

Aplastic/hypoplastic marrow was the second most common finding. Of these, 3 cases showed evidence of PNH clone. None of the 16 cases tested for chromosomal breakage were positive, ruling out Fanconi anaemia.

Erythroid hyperplasia constituted 15% of the total cases. Four cases of haemolytic anaemia were diagnosed, of which 2 cases were thalassemia major. Nine cases (60%) showed megaloblastic maturation of the erythroid series. Three marrows showed normoblastic maturation (20%), 2 marrows showed a dimorphic picture (13.33%) and 1 marrow showed micronormoblastic maturation (6.66%).

Fourteen bone marrows (14%) showed findings consistent with peripheral destruction of platelets. Platelet counts of these children ranged from 5 - 90 × 10^9 /L. Eight of them (57.14%) showed a platelet count of less than 20 × 10^9 /L. All the biopsies showed an increase in megakaryocyte number, with mostly mature and immature forms (12/14). One case showed dysplastic forms of megakaryocytes and one case showed normal forms. The erythroid series was hyperplastic in 64.29% of the samples, possibly secondary to the anaemia following blood loss.

Eleven cases of storage disorders were diagnosed, of which, the number of Niemann-Pick disease and Gaucher's disease were 5 each (45.45%). This classification was done morphologically, based on the presence of foamy macrophages in Niemann Pick disease, and the crumpled paper appearance of the cytoplasm of Gaucher cells. One case was of GM1 gangliosidosis, which was confirmed on enzyme studies. Three patients were found to have deficiency of β-glucosidase enzyme, confirming Gaucher's disease. Out of these 3 patients, two underwent molecular genetic analysis and were found to have mutation in the GBA gene. Two cases had deficient activity of acid sphingomyelinase, confirming the diagnosis of Niemann-Pick disease. Other diseases diagnosed in our study included changes consistent with hypersplenism, HIV related changes, myelodysplastic syndrome, myelofibrosis secondary to rickets and granulomatous reaction.

Five biopsies in the study showed normal histology.
Fourteen of the 100 cases were labelled as dry tap on BM aspirate examination. Of these, 4 cases showed hypercellularity with fibrosis, 4 cases showed only hypercellularity and 3 cases showed only fibrosis. The other 3 cases showed neither hypercellularity nor fibrosis.

DISCUSSION:

The objective of this study was to observe the frequency of various haematological and non-haematological disorders diagnosed on bone marrow examination in children in our hospital.

The general epidemiological parameters in our study were consistent with similar studies conducted in other parts of the world [2], [5], [6]. Among the clinical presentations, the commonest finding in our study was fever, followed by pallor, as was also reported by Ali et al [7] and Baichoo et al [4]. Khan et al [6] found that pallor and bleeding

manifestations were the most common clinical features in the children undergoing bone marrow examination. The common indications for performing the procedure were similar in all the studies even if slight variations in frequency can be observed [5]. The commonest diagnosis in the bone marrow biopsies in the present study was acute leukaemia (28%), followed by aplastic anaemia (20%). In the study by Ali et al [7], the most common diagnosis given was nutritional anaemia. The main findings in the study by Baichoo et al [5] were neoplastic disorder, reactive marrow, nutritional anaemia and ITP. Khan et al [6] reported aplastic anaemia as the most common finding.

Among the 14 dry taps, the maximum number of cases were of acute leukaemia (50%). Ahmad et al [8] stated that dry tap is generally attributed to conditions which result in either fibrosis or hypercellularity or both. The common diseases resulting in dry tap include leukaemia, lymphomas, drug toxicity, Gaucher disease, and normal marrows [9]. It is proposed that even normal findings on biopsy following a dry tap aspiration might imply marrow pathology, which may have been missed due to patchy involvement of the marrow.

Acute leukaemia: Considering the individual conditions, Acute leukaemia was the most common diagnosis given on bone marrow biopsy in our study. The distribution of these into ALL and AML was similar to that reported by Baichoo et al, Hussain et al [2] and Ali et al [7] in their respective studies. Arora et al [10] found that in India, 60-85% of all leukaemia reported are ALL. According to the literature review of the epidemiological burden of ALL by Radaelli et al [11], the incidence shows a bimodal distribution, with a high peak early in life, followed by another much lower peak after age 70. Yasmeen et al [12] reported that the patients in their study were brought in with a wide spectrum of symptoms and duration and fever was the most common presenting complaint seen in 95% patients.

The 20 cases of ALL in our study were classified into L1, L2 and L3 based on the scoring system by Bennett et al [13]. Based on this scoring system, 11 ALL cases (55%) were classified as ALL-L1, 6 cases (30%) were classified as ALL-L2 and 3 cases (15%) were classified as ALL-L3. Although this morphological classification does not hold much significance with the advent of more sensitive diagnostic tools, it can be valuable in guiding the initial treatment in a resource limited setting and/or till the flowcytometric and molecular analysis is done. In a study of bone marrow fibrosis in ALL of childhood by Hann et al [14], 57% of marrows were found to have significant fibrosis. As for AML, Ali et al [7] reported 40% of the total leukaemia cases in their study to be of AML. It was more commonly found in males (4/6) and equally found in the age group of 1 to 3 years and 6 to 11 years (2 cases each). In a study by Afridi et al [15], AML was most common in the age group of 1 to 5 years and was more common in males. They reported fever, bleeding, pallor and splenomegaly as the common clinical presentations of AML in their study.

Aplastic anaemia (AA): Defined as pancytopaenia with a hypocellular bone marrow in the absence of an abnormal infiltrate with no increase in reticulin [16], it was the second most common finding in the present study (20%). According to the guidelines for the diagnosis and management of aplastic anaemia [16], there is biphasic age distribution of aplastic anaemia with peaks from 10 to 25 years and 60 years. The incidence of males and females is equal. Patients with aplastic anaemia most commonly present with symptoms of anaemia and skin or mucosal haemorrhage [16]. BM trephine biopsy is the most important test for diagnosis of AA, the hallmark being the reduction of the haematopoietic cellularity below 30%. BM aspiration does not necessarily allow a correct quantification of the haematopoietic cellularity [17]. It is, however, useful for the detection of dysplastic and blast cells thus supporting differential diagnosis with MDS and hypocellular leukaemia [16]. A 'hot spot' in a patchy area may explain why sometimes the aspirate is normocellular. Up to two thirds of patients with pancytopaenic AA concomitantly have small clones of PNH cells, and about 30% of patients with PNH have preceding AA [17].

Erythroid hyperplasia: Erythroid hyperplasia constituted 15% of the total cases. Ali et al [7] found the most common etiology in paediatric age for erythroid hyperplasia to be nutritional anaemia; the age and sex distribution and the clinical findings were comparable with our study. Baichoo et al [5] found that nutritional anaemia constituted 8.5% of the total number of cases undergoing bone marrow biopsy. The study of 89 cases by Parajauli et al [19] in Nepal showed megaloblastic maturation to be more common than micronormoblastic maturation.

Peripheral destruction of platelets: Fourteen of our cases (14%) were diagnosed as consistent with peripheral destruction of platelets indicating Immune thrombocytopenic purpura (ITP). Based on international consensus, ITP should only be diagnosed if the platelet counts are repeatedly below 100×10^9 /L. In children and adolescents, the ITP incidence is 0.2 – 0.7 new cases per 10,000 per year and the prevalence is 0.4 – 0.5 per 10,000. In paediatric ITP, boys are more often affected than girls [20], as was also seen in our study. In the study by the intercontinental cooperative immune thrombocytopaenia study group [21], cutaneous bleeding was the most common form of bleeding amongst children. A platelet count of less than 20×10^9/L is more common in children (79%) than in adults [20]. They found that the mean platelet count at diagnosis was 18.1×10^9 /L for children. The morphologic changes in megakaryocytes observed are immature forms (63.6%), micromegakaryocytes (18.1%), hypolobated forms (9%) [22]. In the megakaryocytic alterations in thrombocytopenia studied by Muhury et al [23], 19 cases of ITP were studied. Of these cases, 18 bone marrows showed an increase in the number of megakaryotes, while megakaryocytes were normal in 1 case. Dysplastic forms were seen in 17 cases (89.5%), bare megakaryocytic nuclei in 16 cases (84.2%) and micromegakaryocytes in eight cases (42.1%).

Storage disorders (SD): Storage disorders are caused by deficiencies of one or more enzymes required for the catabolism structurally complex biomolecules, including proteins, nucleic acids, sphingolipids, neutral lipids, and glycogen; arising from the normal turnover of the cellular constituents. They are often classified according to the principal substrate of the deficient enzyme [24]. Pradhan et al [24] classified the lysosomal storage disorders into Gaucher's and non-Gaucher's disease based on the morphologic variations seen on bone marrow examination. They found the peak age group to be 1 to 2 years (68%) with a male preponderance. Patients presented with abdominal distension due to hepatosplenomegaly and neurologic symptoms in the form of developmental delay and seizures. 56% cases were non Gaucher's and remaining 44% cases were of Gaucher's disease.

Two cases in our study presenting with cytopaenias and splenomegaly showed hypercellular marrow and hyperplasia of all three lineages and hence were diagnosed as Hypersplenism. Sundaresan et al [25] found the common etiology for hypersplenism to be malaria, CML, enteric fever and non-cirrhotic portal hypertension. They found a significant improvement in the CBC levels in patients post splenectomy.

The most common retroviral disease related changes in BM include dysplasia and plasmacytosis which were also found in 2 of our cases. [26], [27].

One case of MDS - excess blasts II was reported. Although uncommon in paediatric age group, MDS shows characteristic morphological features and should be followed up due to its increased chances of progression to AML.

One case of Myelofibrosis secondary to rickets was diagnosed. In rickets, the fundamental morphologic disturbances are failure of calcification of the deepest layer of growing cartilage and osteoid tissue. In addition, varying degrees of fibrosis are present in the marrow tissues which may contain poorly arranged trabeculae of uncalcified osteoid [28]. It is important to diagnose secondary myelofibrosis as the treatment of the underlying condition can lead to the reversal of the condition.

In the present study, a case of tuberculosis was diagnosed as the patient showed granulomatous reaction in the BM biopsy. The conditions leading to granuloma formation in bone marrow include infections like mycobacterium, fungus, typhoid and paratyphoid, and brucellosis. The non-infectious causes include Hodgkin lymphoma and MDS [29].

CONCLUSION:

Our study highlights the wide spectrum of disease entities diagnosed on bone marrow biopsy in the paediatric age group. Thus, despite being invasive, with adequate clinical and haematological correlation, bone marrow examination becomes an indispensable diagnostic tool in several haematological and non-haematological disorders in children.

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