Diagnostic Utility of Bone Marrow Aspiration and Biopsy in Paediatric Age Group

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ABSTRACT

Introduction: Bone marrow examination required for differential diagnosis of various myelo and lymphoproliferative disorders; their prognostic classification and assessment of status during and after therapy, staging of lymphoma and marrow infiltration. Study aimed to evaluate the contribution of bone marrow aspiration and trephine biopsy to the final diagnosis.

Material and methods: Two and half year study of BM trephine biopsy lesions in pediatric population (0 to 18 yrs). BM biopsy processed with H and E stain and special stains.

Results: maximum cases were male s and from age group of 12-18 yrs, fever is the most common symptom and pallor is most common sign encountered, majority cases were anemias followed by infectious disease, Leukemias and ITP. BM aspiration and BM Biopsy are complimentary to each other in 72.5% cases.

Conclusion: Bone marrow Aspiration and BM Biopsy are confirmative for tissue diagnosis and plays important role is clinical diagnosis, prognosis and also to decide line of management.

Keywords: Pediatric Bone Marrow Aspiration, Bone marrow Biopsy

INTRODUCTION

During the past decades there have been major advances in the understanding of disorders of the blood accompanied by increasing recognition of the complex structural and hormonal interrelations between the cellular and tissue elements of the marrow. Improvements in biopsy technique as well as technical progress in their preparation have provided additional impetus to the study of the bone marrow as an organ with architecture and components intact in their natural spatial context.[1] The indications stem from many fields including hematology, immunology, oncology and rheumatology. Improved needles permit the simultaneous performance of aspiration and biopsy. The former is particularly useful for cytological details, cyto-chemical stains and immunological markers while the latter permits a complete assessment of marrow architecture. In hematology, bone marrow examination is needed for the differential diagnosis of various myelo- and lymphoproliferative disorders; their prognostic classification and assessment of status during and after therapy, staging of lymphomas and marrow infiltration by foreign cells.[1-3] In this study we aim to demonstrate the utility of the bone marrow trephine biopsy, assess its contribution to the final diagnosis in the pediatric population and demonstrate the spectrum of lesions encountered in the pediatric age group in a large general tertiary care teaching hospital.

MATERIAL AND METHODS

This study comprises a two and a half year study of bone marrow trephine biopsy lesions in the pediatric population (age group 0 to 18 years) in Grant Medical College and Sir J.J. Hospital Mumbai. Total 120 cases were included in the study based on the inclusion and exclusion criteria. Institutional ethical committee has approved the study. A detailed clinical history, general and systemic examination were noted and this information was recorded in the Performa. Every case is investigated with peripheral blood smear, complete blood count along with haemotological parameters like bleeding time (BT), clotting time (CT), aspiration and bone marrow biopsy. A written informed consent was taken in all cases. A bone marrow aspiration and biopsy from the posterior superior iliac supine were done using the aspiration needle and Jamshidi needle respectively. The bone marrow aspiration needle no 18 was introduced and when the marrow cavity was entered, a 20 cc plastic syringe was attached to the needle after withdrawing the stiletto and suction was applied to obtain the bone marrow aspirate. Smears were made of the aspirate immediately and stained with Leishman's stain. A small nick was made with the scalpel blade and the Jamshidi needle (No.11) with the stillete locked in place was advanced through the lesion pointing in the direction of anterior superior iliac supine into the bony cortex into clockwise and anticlock wise motion was made to obtain the bone marrow core. the needle was rotated completely several times along its long axis and removed with alternating rotary motions. Gauze was held at the biopsy site giving pressure for a few minutes. The biopsy specimen was expelled through the proximal end. It was put in buffered formalin fixative and taken for routine processing. In all cases routine H and E stain was done. Special stains, like Reticulin stain, Masson Trichrome and Prussian Blue were done wherever necessary.

STATISTICAL ANALYSIS

Descriptive statistics like mean and percentages were used to interpret results.

RESULTS

This was two and half years prospective study of bone marrow trepine biopsy lesions encountered in the pediatric population.

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An analysis of the age distribution pattern indicates that the maximum number of cases was in older age groups, the maximum being 57/120 cases (47.5%), in oldest age range of 12-18 years. This was followed by the age range 5-12 years i.e. 31/120 cases (25.83%) and 1-5 years 28/120 cases (23.33%). The minimum number of cases 4/120 (3.3%) were in the age group of less than 1 year. No neonates were encountered in the study. The sex distribution pattern indicates a higher percentage of males 75/120 cases (62.50%) compared to females 45/120 cases (37.5%). Male to female ratio being 1.66.An analysis of clinical symptomatology indicates that the fever was the commonest symptom encountered, seen in 68/120 cases (56.6%) followed by general debility – 46/120 cases (38.3%). GI disturbances like anorexia, nausea, abdominal distension, and bleeding tendencies were the next most commonly seen symptoms 29/120 cases (24.2%) and 22/120 cases (18.3%) respectively. The various types of bleeding tendencies encountered were epistaxis, bleeding gums, malena, hematemesis, hemoptysis, menorrhagia, ecchymotic patches and the commonest was epestaxis. The least frequently encountered symptoms were pica and amenorrhea cases 1/120 (0.8%). An analysis of the signs elicited recorded that pallor was the commonest clinical sign encountered – 112/120 cases (93.3%) cases. The sites of pallor being conjunctiva, tongue, palm etc. this was followed by hepatosplenomegaly seen in 34/120 cases (28.3%) cases. The next commonest sign encountered was isolated splenomegaly 18/120 cases (15%). This was followed by icterus 13/120 cases (10.8%) and edema 12/120 cases (10%). The commonest site of edema was feet. The least frequent elicited sign was sternal tenderness 4/120 cases (3.33%). A broad analysis of the combined findings of the peripheral smear, bone marrow aspirates and trephine biopsy showed that the majority of cases were of anemias 74/120 cases (61.66%). This was followed by infectious diseases 14/120 cases (11.66%). We encountered only 10 cases of leukemias and ITP each (8.33%). Of the 10 cases of leukemia, 8 were ALL, 3 being L1 and % L2 and 2 were AML- one being M4 and other M6. Split up of ITP was – 8 cases of acute ITP and 2 of Chronic ITP. We encountered 4/120 cases (3.33%) of marrow eosinophilia which were clinically diagnosed as hypereosinophilic syndrome. The least frequently encountered lesions were metastasis, storage disorders, myelofibrosis and hypersplenism 2/120 cases each (1.66%). The metastasis seen were both from malignant small round cell tumor i.e. neuroblastoma and PNET. The storage disease split up was – one case of Gaucher's and one case of Niemann Pick disease each the 2 cases of myelofibrosis included 1 primary and the other secondary to Hodgkin's disease. Both the cases of hypersplenism were secondary to pancytopenia. Of the 74 cases of anemias the majority i.e. 45/74 cases (60.81%) were dimorphic anemias followed by iron deficiency anemias 10/74 cases (13.51%), This was followed by haemolyticanemias 9/74 cases (12.16%), the subgroups being thalassemia 4/9 cases (44.44%), sickle cell disease 2/9 cases (22.22% and elliptocytosis 1/9 cases (11.11%); the cause of the other two was unknown. Hypoplastic/aplastic anemias constituted 7/74 cases (9.45%). Pure megaloblastic anemia was infrequently encountered 3/73 cases (4.05%). An analysis of the spectrum of infections encountered reveals that in the majority of cases the cause was non specific with marrow showing evidence of myeloid hyperplasia 6/14 cases (42.9%). Specific infections like malaria and kala-azar were seen in 4/14 cases (28.6%) and 3/14 cases (21.4%) respectively. We had a single rare case of haemophagocytic syndrome (7.1%). Correlation of the clinical diagnosis and bone marrow diagnosis showed that in the majority of cases 57/120 cases (47.5%) the aspirate and biopsy both confirmed the clinical diagnosis. The biopsy and or aspirate alone gave the diagnosis in a significant 51/120 cases (42.5%) while it was non contributory in a smaller number of cases i.e. 12/120 cases (10%) where the biopsy was inadequate. A comparative evaluation of bone marrow aspiration and biopsy showed that both the procedures were complementary to each other in majority of the cases – 87/120 (72.5%) the bone marrow trephine alone gave diagnosis in 17/120 cases (14.16%) the majority of which yielded a dry tap on aspiration either due to hypocellular marrow the cause being0hypoplastic anemia, myelofibrosis; or hypercellularmarro as in the cases of leukemia and metastasis. The aspirate was dilute in a few cases and thus inconclusive for opinion. Bone marrow aspirate alone gave the diagnosis in 16/120 cases (13.33%). Out of these 16 cases, in 12 cases biopsy was inadequate; two cases were of kala-azar and two of malaria where the LD bodies and schizonts could not be detected on the trephine biopsy.

DISCUSSION

In recent years, the indications for bone-marrow biopsy have broadened so that they have now been employed in the investigation of many disorders in hematology, internal medicine, oncology and osteology. The upsurge of interest was spurred by improvement in instrumentation for taking the bone marrow biopsy as well as in processing techniques.The most frequent indication for bone marrow examination was unexplained anemias – 42/120 cases (35%) with or without organomegaly mainly hepatosplenomegaly – 18/120 cases (15%) and PUO – 6/120 cases (5%). This contrasts with the study of Githang et al[3] who got the maximum number of requisitions for bone marrow examination for hematological and non-hematological malignancies – 46%. We encountered only 10 cases of leukemias, 8.33% out of which 8 were ALL constitutes 85% of childhood hematological malignancies and AML – 15%, Miller et al[2] However the study of Hasenbegvoic et al found[4] an equal frequency of ALL and AML and a lower percentage of leukemias – 2.66% compared to our figure of 8.33%. one of the patients presented with pancytopenia (subleukemic leukemia) and bone marrow aspirate and biopsy confirmed the diagnosis. Out of 8 cases of ALL, 3 were L1 (27.5%) and 5 were L2 type (72.5%); here the proportion is in reverse compared to literature which states that the percentage of LI is higher, but this variation can be because more of our patients were in older age group as this fact is well documented by the study of Vienna MB[5] and Lilleyman JS[6] who found that an age more than 10 years was associated with L2 and a poorer prognosis. 2 of our patients were diagnosed as AML the subtype being – M4 and M6 – one case each. Neither of these cases were clinically suspected as AML; the clinical suspicion being CML in one case and ITP/ aplastic anemia in other because of confusing clinical features and ultimately the bone marrow examination gave the diagnosis. According to Caplin C et al,[7] the risk of missing leukemias in patients having typical features

of ITP is less than 1% and they did not find even a single such case in a study of 332 cases who presented with ITP like features. But we found one such case. Batra et al[8] have also described bleeding manifestations and thrombocytopenia of short duration in ¼ (25%) of in the pediatric age group constituting only 2-7% of AML cases, the clinical presentation being similar to adult patients. We did not encounter a single case of described in the literature- Hann et al.[9] We encountered 10 cases – 8.33% of ITP and subcategorized these into acute – 8 cases and chronic – 2 cases. All the patients were under 15 year of age. This is in correlation with the literature 2 which describes acute ITP in children more frequently compared to adults and chronic ITP more frequently in adults. There were 4 cases showing eosinophilia in the peripheral blood and clinically suspected to be having hypereosinophilic syndrome; all the 4 demonstrated marrow eosinophilia on aspirate as well as trephine biopsy, thereby confirming the clinical diagnosis. The least frequently encountered lesions were matastasis, storage disorders, and myelofibrosis and hypersplenism – 2/120 cases each – 1.66% Of the 2 cases of metastasis one was secondary to neuroblastoma and the other secondary to PNET. 50% cases bone marrow aspirate and biopsy gave the diagnosis and in the other 50% it was only the biopsy that gave the diagnosis as the aspirate was a dry tap. In the study of Penchansky et al,[10] a similar result was obtained, in which half the number of cases required bone marrow aspiration and bone marrow biopsy for the diagnosis and the other half were diagnosed only by the bone marrow trephine biopsy, emphasizing the fact stressed in the literature that both these procedures are complimentary in the workup for metastasis-Penchansky et al.[10] This study also emphasizes that no single hematological parameter is predictive of bone marrow metastasis, but these authors found that the percentages of Hb and platelet count pancytopenia with a haemoglobin value of 6 gm% and the other one showed microcytic hypochromic anemia, with a haemoglobin value of 9.5 gm%.

There were 7 cases clinically suspected to be lymphoma but none showed bone marrow involvement. Bone marrow metastasis was also not detected in a clinically diagnosed case of soft tissue sarcoma. Thus out of the total 10 cases of non hematological malignancies only two (20%) showed bone marrow involvement. This figure is slightly higher than that of Valdes S. M.et al[11] who detected bone marrow involvement in 17.5% cases, of non hematological malignancies. The series of Penchansky et al[10] however found evidence of matastasis in a very high percentage of cases-45 percent in their series of non- hematological malignancies. We encountered two cases of storage disorders; the patients presented with hepatosplenomegaly and were clinically suspected to be having a storage disorder. The bone marrow aspirate in both the cases was dilute and it was the biopsy which confirmed the diagnosis. One case was diagnosed as Niemann-Pick and the other as Gaucher's. We also encountered two cases of myelofibrosis- one a known case of MDS and clinically suspected to have progressed to CML and the other secondary to lymphocytic depleted Hodgkin's Lymphoma. In both the cases aspirate was a dry tap and the biopsy gave the diagnosis. In the case of Hodgkin's lymphoma, the lymphoma cell however could not be detected as a result of extensive myelofibrosis,studies of bone marrow trephine biopsies in cases of Hodgkin's disease (Mahoney et al)[12] indicate that patients with bone marrow disease have a stage IIIB disease, pre biopsy. Positive bone marrow results do not effect a change in therapy. The small number of positive cases does not allow any prediction as to prognosis and there is no role for bone marrow biopsy with a clinical stage of I-IIIA Hodgkin's disease.

Out of 10 cases of all malignancies that is hematological and non hematological that we encountered in our study. None showed evidence of myelonecrosis while the same is described by Pui CH et al[13] in 0.5% of their patients with malignant diseases. The percentage of leukemic patients showing myelonecrosis is quite high in the study of Prajapati N C et al[14] -6.66%. and they noticed that thrombocytopenia/leucopenia was the common presenting feature.

Out of 74 cases of anemias, the majority were due to dimorphic anemias- 60.81% i.e. a combination of iron deficiency and B12 deficiency anemia showing micronormoblastic and megaloblastic change, this figure is much higher than that of Hasenbegovic et al[4] who found it in only 9.3% of their cases. Pure iron deficiency anemia manifesting as micronormoblastic maturation in the marrow was seen in 13.51% cases, more than the percentage found by Farhi et al[15]-8% but much less than the percentage of Buhr T et al[16]-22.7% and Gomber et al[17] -68.92%, however this percentage includes both a pure and mixed type of iron deficiency anemia. The other group of deficiency anemias i.e. megaloblasticanemias constituted -4.05% of cases, this figure is similar to that of the study of Farhi et al[18] and Buhr T et al[19] who found pure megaloblastic anemia in 4% and 3% of their cases respectively, but higher than the figure of Hasenbegvoic et al[4] who found in only 1.3% of his cases. The study of Gomber et al[17] however found a much higher percentage of 28.42% cases but this includes both pure and mixed type of B12 deficiency. We encountered 12.16% cases of hemolytic anemias, more than the percentage of Buhr T et al[19] -7.2%. The subgroups of hemolytic anemia being four cases of thalassemia, two cases of sickle cell disease, one case of elliptocytosis and unknown causes in the other biopsy. Aplastic / hypoplasticanemias constituted – 9.45% of anemias is higher than the – 6.8% found by Buhr et al.[18] The cases of aplastic/ hypoplasticanemias- showed evidence of pancytopenia on the peripheral smear, the aspirate showed a dry tap except in one case and it was the trephine which confirmed the diagnosis. This compares well with study of Gruuppo et al[19] who found bone marrow trephine biopsy to be an important and reliable indicator of marrow cellularity as compared to aspiration in diagnosing aplastic anemias and leukemias.

Out of the 120 cases studied in 12 cases -10% the biopsy was inadequate for conclusive interpretation, this figure is much lower than that of Patricia et al 120 and Reid et al[20] 17% and 13% respectively.

A correlation of the clinical diagnosis and bone marrow biopsy diagnosis indicated that in the majority of cases 57/120- 47.5% the biopsy confirmed the clinical diagnosis. The biopsy alone gave the diagnosis in a significant number-51/120 cases-42.5% while it was non contributory in a smaller number of cases in 12/120 cases-10%. In these cases the biopsy was inadequate for reporting.

A comparative evaluation of bone marrow aspiration and biopsy showed that both the procedures were complimentary to each other and both gave the diagnosis in a high percentage of 72.5%

this is similar to the findings of Nanda et al[18] who made the diagnosis by aspirate and biopsy also in a high percentage of 88.6% cases. The bone marrow trephine biopsy alone gave the diagnosis in 17/120 cases- 14.16%, a figure slightly higher than that of Nanda et al[21] – 11.4. The bone marrow aspirate alone gave the diagnosis in 16/120 cases, out of these 16 cases, biopsy was inadequate in 12 cases, 2 cases were of malaria and 2 of kalaazar where the LD bodies and schizonts could not be detected on the trephine biopsy. Thus the bone marrow trephine biopsy should not be taken as a substitute but as a complimentary procedure to aspirate to enhance the yield of the diagnosis.

CONCLUSIONS

Bone marrow Aspiration and BM Biopsy are confirmative for tissue diagnosis and plays important role is clinical diagnosis, prognosis and also to decide line of management.

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