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Evaluation of Clinical Indications and the Reviewed Diagnoses from Bone Marrow Aspirate Examinations in Paediatric Patients at a Central Hospital in Zimbabwe

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Case Report

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Abstract

Objectives: To evaluate the correlation between clinical suspicion and the final laboratory diagnosis after the bone marrow examination

Design: A 6year retrospective cross-sectional study

Setting: Parirenyatwa Group of Hospitals, Zimbabwe

Subjects: Seventy-six pediatric bone marrow aspirate (BMA) examination cases from 2016 to 2022 that had data that suited the study available were included in the study.

Results: The 76 case participants had median age of 7 (age range 1-12). Six-two (81.6%) cases were found to have a complete BMA examination report while fourteen (18.4%) cases had technical errors reported and therefore excluded from the analysis of case results. Amongst the 14 excluded cases; 10(71.4%) were reported as unsuitable for diagnosis and 4(28.6%) reported as haemodilute for diagnosis. The triggers for BMA examination were grouped as; aplastic anaemia 5(6.6%), anaemia with variations 21(27.6%), pancytopenia 14(18.4%), and suspected haematological malignancies 36(47.4%). Analysis of the complete 62 case reports found; 34(54.8%) haematological malignancies, 2(3.2%) no diagnostic features, 5(8.1%) aplastic anaemia, 17(27.4%) no evidence of neoplasm/ infiltration, 3(4.8%) bone marrow hypoplasia, and 1(1.6%) non haematological metastasis. The percentage diagnostic yield between triggers for BMA examination and the BMA examination reports was 62/76 (81.6%0. However, there was no statistically significant correlation (p=0.275) to conclude that there is concordance between triggers for BMA examination and BMA examination diagnosis.

Conclusion: Haematological malignancies were the commonest triggers for BMA examination in this study. Haematological malignancies were also found to be the commonest outcome in BMA reports done in pediatric patients with the major form being all.

Keywords: Bone marrow aspirate, haematological malignancies, leukemia, anaemia, pediatrics

Abbreviations: BMA: Bone marrow aspirate; PGH: Parirenyatwa Group of Hospitals; JREC: Joint Research Ethics Committee; FISH: Fluorescence In-Situ Hybridization; HIV: Human Immunodeficiency Virus.

Introduction

There are a few haematological disorders whose diagnosis can be revealed using a bone marrow aspirate examination.

Bone marrow is the viscous tissue found in the confines of the long bones. The bone marrow contains haematopoietic cells, composed in their majority by haematopoietic precursors of the megakaryocyte lineages [1]. Haematological disorders arise mostly due to problems originating from the bone marrow stem cells and microenvironment.

Examination of the bone marrow can help in the diagnoses of many haematological disorders and gives a comprehensive intel on the disorder being investigated and it has been extensively revised to reflect the significant advances that have occurred in molecular biology and genetics [2] Some of the triggers for BMA examination include; diagnostics of unexplained fevers, hepatosplenomegaly, haematological malignancies, follow up after and during chemotherapy and assessment of iron level if biochemical iron studies are not conclusive. Staging of certain malignancies is also a common reason for bone marrow examination [3].

Bone marrow aspirate examination can reveal a normal picture, dry tap, haemodilute or bone marrow infiltration and each of these has its own contributions to the report and ultimately patient care. A haemodilute BMA may be difficult to analyse for the haematologist and unsuitable leading to a delayed diagnosis for the patient, which may lead to further progression of the disease. Pediatric patients differ from adults anatomically and physiologically in various ways, which requires special skill when analysing their bone marrow abnormalities. The results from bone marrow examination may vary from one case to another depending on the clinical indication or suspected condition [4].

Bone marrow examination is the pathological analysis of a bone marrow resemblance acquired through bone marrow biopsy and or bone marrow aspirate. Several staining techniques are used for examination on a microscope. A bone marrow biopsy is a cut section of the bone that contains marrow in it. A bone marrow aspirate is a small amount of bone marrow fluid and cells removed from the bone marrow through a needle. It is also used in follow-up of patients with haematological diseases and for investigating various non-haematological conditions including storage diseases, inborn errors of metabolism, metastatic cancer, and infection that has spread to the bone marrow [2].

Materials and Methods

Demographic and BMA examination data for pediatric patients at Parirenyatwa Group of Hospitals (PGH) medical records were collected and captured directly into an excel sheet. The study cases were from pediatric patients (less than 12 years old) who had a bone marrow examination done between 2016 and 2022 and their demographics and BMA results available.

Data collected were stored on an encrypted excel sheet and patients were assigned a code for confidentiality and security. The data were retrieved from files of request forms in which bone marrow examination results are stored. All results and request forms for BMA are stored in the Haematology department at PGH. The forms were taken and all pediatric request forms that met the criterion of the study were put aside for capturing into an excel document. Each request form was filed accompanied by a result sheet. The request forms selected included the following indication for BMA examination, age, and thesuspected condition if available. Convenience sampling method was used in the collection of data, depending on the ward of admission, age and consideration of the inclusion criterion.

Approval to carry out the research study was sought from the Department of Laboratory Diagnostics and Investigative Sciences, Medical Laboratory Sciences unit, Faculty of Medicine, and Health Sciences at the University of Zimbabwe. Permission to conduct the study was sought from the respective management. Clearance on ethics of the study was sought by application to the Joint Research Ethics Committee (JREC Ref: 65/2022) to obtain approval. Access to subject information was strictly available only to the researchers.

Diverse clinical indications such as; pancytopenia, anaemia, concern for lymphoma, anaemia with thrombocytosis, aplastic anaemia, anaemia with lymphocytosis, bicytopenia and concern for haematological malignancy, were extracted from the records of bone marrow examinations.

The reviewed final laboratory diagnoses were classified into either complete or incomplete reports. The complete reports were those BMA examination results that could be used for patient management. Incomplete reports were those which were found to be unsuitable for reporting and a repeat sample recommended due to procedural or technical errors. The suspected conditions or clinical indications were matched with the final reviewed laboratory results. These were grouped into discordant and concordant. The discordant results are those that were found not matching the clinical suspicion. The matching results are those that had a positive result after having a bone marrow examination reviewed.

The Graph Pad prism 9 program and Microsoft excel were used for data analysis that included descriptive statistics (percentage, range, mean and standard deviation) and comparisons according to the distribution of the data in all variables. A Chi-Square test was used to determine association at p less than 0.05 significance level.

Results

Case Characterization

A total of 76 cases were recruited for the study based on the selected criterion. Amongst the cases 57% (43) were males and 43% (33) were females. In 76 cases 62 (81.6%) were found to have a complete BMA examination report. Fourteen (18.4%) cases were excluded from the analysis of laboratory results due to technical errors reported from the Bone marrow examination. Amongst the 14 cases 10 (71.4%) had BMA results reported as unsuitable for diagnosis and 4 (28.6%) were reported as haemodilute for diagnosis.

Age Range	1 - 12yrs
Median Age	7 years
Gender	Males 43(57%) Females 33(43%)
	n= 76

Table 1: Statistical Summary of Case Demographics.

Clinical Indication/Suspected	Frequency	% Within Subgroup	%(n=76)
A. Pancytopenia (n=14)			
Pancytopaenia	14	100%	18.40%
Pancytopenia	**14**	**100%**	**18.40%**
B. Haematological malignancy (n=36)			
Concern for non hodgikins lymphoma	2	5.50%	2.60%
Concern for Lymphoma	1	2.80%	1.30%
Concern for Leukaemia	5	13.90%	6.60%
Concern for haematological malignancy	9	25%	11.80%
Concern for Acute Lymphoid Leukaemia	13	36.10%	17.10%
Chronic myeloid leukaemia	1	2.80%	1.30%
Lymphadenopathy	3	8.30%	3.90%
Acute myeloid leukaemia	2	5.50%	2.60%
Haematological malignancy	**36**	**100%**	**47.40%**
C. Aplastic anaemia (n=5)			
Aplastic Anaemia	5	100%	6.60%
Aplastic Anaemia	**5**	**100%**	**6.60%**
D. Anaemia with variations (n=21)			
Anaemia with Thrombocytosis	2	9.50%	2.60%
Anaemia with Leukocytosis	4	19%	5.30%
Anaemia with bleeding	3	14.30%	3.90%
Anaemia with lymphocytocis	1	4.80%	1.30%
Severe anaemia	2	9.50%	2.60%
Anaemia with bicytopenia	1	4.80%	1.30%
Anaemia	8	38%	10.50%
Anaemia with variation	**21**	**100%**	**27.60%**
Total	**76**		100%

Table 2: Frequency of Clinical Indication in 76 Cases Recruited into the Study.

The clinical indications for BMA examination for all 76 cases were grouped into 4 groups (Table II); a) pancytopenia with 14(18.4%), b) haematological malignancies with 36(47.4%), c) Aplastic anaemia with 5(6.6%), d) anaemia with variation 21(27.6%).

Reported As	Frequency	Percentage
Acute Myeloid Leukaemia	2	3.20%
Acute Lymphoid Leukemia	28	45.20%
Aplastic anaemia	5	8.10%
Bone marrow hypoplasia	3	4.80%
Chronic Myeloid Leukaemia	2	3.20%
Non haematological bone marrow metastasis for further Subtyping	1	1.60%
Bone marrow infiltrated by primitive Haematological Malignancy	1	1.60%
No diagnostic features	2	3.20%
No evidence of bone marrow infiltration/Evidence of neoplasm	17	27.40%
Acute promyelocutic Leukaemia	1	1.60%

Table 3: Characterisation of the reviewed final laboratory Diagnosis after the BMA examination in 62 cases.

- **Frequency:** Is the number of cases that were found to have a specific condition in the reviewed diagnosis.

In the analysis of 62 laboratory results (Table 3), 34(54.8%) were found to have haematological malignancies, 2(3.2%) had a BMA with no diagnostic features, 5(8.1%) had aplastic anaemia, 17(27.4%) had no BMA infiltration/ no evidence of neoplasm, 3(4.8%) bone marrow hypoplasia, and 1(1.6%) with non haematological bone marrow metastasis.

Suspected Condition Or Clinical Indication	Frequency	Percentage Concordant	Percentage Discordant
Anaemia with lymphocytosis	1	1(100%)	0(0%)
Anaemia with bleeding	3	1(33.3%)	2(66.7%)
Anaemia with Leukocytosis	4	4(100%)	0(0%)
Anaemia with bicytopenia	1	1(100%)	0(0%)
Anaemia with thrombocytosis	2	0(0%)	2(100)
Aplastic Anaemia	3	1(33.3%)	2(66.7%)
Pancytopenia	10	3(30%)	7(70%)
Severe anaemia	2	1(50%)	1(50%)
Anaemia	6	4(66.7%)	2(33.3%)
Concern for Acute Lymphoid Leukemia	10	8(80%)	2(20%)
Concern for haematological malignancy	7	4(57.1%)	3(42.9%)
Concern for Leukaemia	4	3(75%)	1(25%)
Chronic myeloid leukaemia	1	1(100%)	0(0%)
Acute myeloid leukaemia	2	2(100%)	0(0%)
Jaundice and generalized Lymphadenopathy	1	0(0%)	1(100%)
Bleeding and lymphadenopathy	2	0(0%)	2(100%)
Concern for Lymphoma	1	0(0%)	1(100%)
Concern for non-Hodgkin's lymphoma	2	0(0%)	2(100%)

Table 4: Diagnostics matches for the 62 cases that had a reviewed final laboratory diagnosis.

- **Concordant -** Bone marrow aspirate results that had a suspected diagnostic outcome similar to the suspected condition or clinical indications.
- **Discordant -** Bone marrow aspirate results that did not match the suspected condition or clinical indications
- **Frequency and Percentage -** total number of bone marrow aspirates done per indication or suspected condition and percentage in a total of 62. This Table only represents cases that had a conclusive BMA result.

Chi Square test

There was not enough statistical evidence (p=0.275; from the calculation with the data in Table 5) at 0.05 significance level to conclude that there is concordance between clinical indication or suspicion and Laboratory BMA diagnosis.

Suspicion Or Indication	Concordance O *(E) **[X]	Discordance O *(E) **[X]	Totals
Haematological Malignancy	18 *(15.90) **[0.28]	11 *(13.0) **[0.34]	29
Pancytopenia	3 *(5.48) **[1.13]	7 *(4.52) **[1.37]	10
Anaemia with Variations	12 *(10.97) **[0.10]	8 *(9.03) **[0.12]	20
Aplastic anaemia	1 *(1.65) **[0.25]	2*(1.35) **[0.31]	3
Total	34	28	62

Table 5: Grouped suspicion against concordance or discordance to a haematological disorder for 62 cases with complete laboratory reports.

- This contingency Table provides the following information: the observed cell totals- O,
- *(the expected cell total; Expected -E) and the **[Chi-square statistic for each cell- X].

Discussion

A retrospective study of 76 pediatric bone marrow examination reports was carried out to evaluate the correlation between clinical suspicion and the reviewed laboratory diagnosis. Medical records for the cases were analysed and summarized statistically. The study was done at Parirenyatwa Group of Hospitals. The median age of the study participants was 7 years with an inclusive age range of 1 to 12 years. Most of the cases were bone marrow aspirate performed after the age of 6 and this was after presenting with a range of indications repeatedly that led to the bone marrow aspirate being done. Forty-three (57%) of the cases were males and 33 (43%) females.

Out of the 76 cases that were recruited into the study, 62 (81.6%) of them had a diagnostic contribution to the case's haematological profile. The remaining 14(18.4%) had incomplete laboratory reports due to technical errors. If a bone marrow aspirate specimen is found to be giving an undesired result, the search for the disease-causing agent has to be found elsewhere. However, the patient would have already incurred a cost on the procedure that turned out to be of little or of no use. This means that there was extended investigation time and increased cost in both cases of incomplete reporting and those that were found with no disorder. The hospital stay for these cases is also extended including the cost of the stay in hospital.

Four groups of the triggers for BMA examination were created as follows; 5(6.6%) aplastic anaemia, 21(27.6%) anaemia with variation, 14(18.4%) pancytopenia, and 36(47.4%) with suspected haematological malignancies. This distribution confirms the investigation of haematological malignancies as the most common trigger. It also demonstrates that Zimbabwe (a low-income country) has an increasing prevalence of haematological conditions in pediatrics. However, other than BMA examination there are other more accurate diagnostic methods that could have been used such as; flow cytometry, immunohistochemistry, molecular genetics, fluorescence in situ hybridization (FISH) and cytogenetics. Unfortunately, PGH did not have those methods during the period studied, which could have reduced the probability of having a BMA examination for morphology as the sole investigative tool.

The burden of anaemia in pediatrics was also evident in the study with a cumulative proportion of 52.6% (aplastic anaemia, pancytopenia and other anaemias) of the cases. Similar trends have been reported in other studies from the region, for example a study done in South Africa concluded that pancytopenia and B cell lymphoma were indications of the highest frequency with 47.8% and 21.7% respectively5. However, there are many factors that can be attributed to the development of pancytopenia in pediatrics such as; infections (including HIV), malnutrition and mutations6. Despite concerted efforts in the fight against HIV, Zimbabwe remains burdened by this problem.

The 62 complete laboratory reports in our study comprised of; 34(54.8%) haematological malignancies, 2(3.2%) with no significant diagnostic features, 5(8.1%) aplastic anaemia, 17(27.4%) with no evidence of neoplasm or infiltration, 3(4.8%) bone marrow hypoplasia, and 1(1.6%) with non haematological bone marrow metastasis. The 34 haematological malignancies were dominated by acute lymphoblastic leukemia (ALL; contributing 45.2% alone; Table 3). This finding is consistent with the general observation that ALL is the most frequent malignant disease in childhood and adolescence, with an annual incidence of

approximately 3-4 cases per 100,000 children under 15 years of age [7,8].

The concordance analysis between clinical suspicion and the revealed laboratory report was poor (Table IV) in our study, for example; in cases that were suspected to have anaemia with thrombocytosis, aplastic anaemia, and lymphadenopathy had a discordance ranging from 66.67% to 100%. Bone marrow examination can be classified as of poor diagnostic value in cases with a discordance of greater than 50% [5,9-11]. However, the poor concordance in our study could be attributed to the limited diagnostic test available and the fact that some of the indications given were non-specific and could not be followed up since the study was a retrospective design.

In our study setting, the clinical diagnosis (indications), collection of BMA sample, laboratory processing and reporting of the BMA are done by independent professionals. This could be a possible cause for the increased discordance. However, these findings highlight the need for coordinated workflow and more training for the professionals to have a functional system with a better yield and guidelines on the indications for a BMA examination because a standard or improved system would be important in the reduction of human and technical errors.

There was no statistically significant correlation ($p=0.275$) at 0.05 significance level to conclude that there is concordance between triggers for BMA examination and BMA examination diagnosis. Nevertheless, there is need to introduce the monitoring and improved standardization of haematological procedures on the clinical side and quality improvement by the laboratory. Furthermore, 14 (18.4%) of 76 cases that had incomplete results reported as either haemodilute for diagnosis or unsuitable for diagnosis meaning no diagnostic report was issued due to poor sample collection is a cause for concern. Therefore, training of junior clinical staff in bone marrow aspirate collection by qualified haematology specialists to reduce trauma, disease burden and cost to the patient and improve on quality.

Conclusion

Haematological malignancies were the most common indications for a bone marrow examination in our study. Haematological malignancies were also found to be the commonest outcome in the BMA examinations done in pediatric patients with the major form being acute lymphoid leukemia. Although the percentage diagnostic yield between the bone marrow examinations and the clinical indications was 62/76 (81.6%), statistically there was not enough evidence to conclude that there is concordance between clinical indications and BMA examination reports.

Limitations

The sample size between the period January 2016 and January 2022 was affected by the global strike of the covid-19 pandemic which came with lockdowns in the years 2020 and 2021 hence not many bone marrow aspirates were done in 2020 and 2021. The study was done based on available laboratory data as the availability of specialised expertise in bone marrow aspirate and trephine biopsy collection was limited in the years before 2020.There was also no control over the specimen in this study as this was a retrospective design.

Recommendations

Further studies need be done to improve and give a confident diagnostic value to bone marrow examinations in pediatrics. Laboratory personnel should be consistently consulted in the making of the smears and sample collection to improve and reduce the technical errors in the bone marrow aspirates that are collected. The health system also needs improvement in the technical methods of analysis for both laboratory and clinical diagnosis as advancements have been made with regards to bone marrow analysis.

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References

1. Mark CH, Berry R, Holtrup B, Sebo Z, Nelson T, et al. (2017) Bone marrow Adipocytes. Adipocyte 6(3): 193-204.

2. Smita C, Harish C, Sunil S (2010) Bone marrow metastasis by solid tumors-probable hematological indicators and comparison of bone marrow aspirate, touch imprint and trephine biopsy. Hematology 15(5): 368-372.

3. Elmadhoun WM, Noor SK, Bushara SO, Almobarak AO, Husain NE, et al. (2015) Bone marrow aspiration in north Sudan: the procedure, indications and the diagnostic value. Int J Health Sci Qassim 9(4): 434-439.

4. Armstrong N, Hilton P (2014) Doing diagnosis: Whether and how clinicians use a diagnostic tool of uncertain clinical utility. Soc Sci Med 20: 208-214.

5. Tshabalala WS, Pillay S, Wilson D (2020) Diagnostic

outcomes of bone marrow aspirate and trephine biopsies performed at a hospital in KwaZulu- Natal, South Africa. Afr J Lab Med 9(1): 1028

6. Nell EM, Chapanduka ZC (2022) Aetiology of pancytopenia: Experience of a South African tertiary academic centre. Afr J Lab Med 11(1): 1645.

7. Bader P, Locatelli F, Peters C (2022) Paediatric Acute Lymphoblastic Leukaemia (ALL) in Kröger N, et al. (Eds.), The EBMT/EHA CAR-T Cell Handbook 2022 Feb 7. Cham Springer, New York, USA pp: 221.

8. Ali ZM, Hosseini N, Sadeghipour A (2009) Indications and diagnostic utility of bone marrow examination in different bone marrow disorders in Iran. Lab Hematol 15(4): 38-44.

9. Bashawri LA (2002) Bone marrow examination. Indications and diagnostic value. Saudi Med J 23(2):191-196.

10. Quesada AE, Tholpady A, Wanger A, Nguyen AN, Chen L (2015) Utility of Bone marrow examination for workup of fever of unknown origin in patients with HIV/AIDS. J Clin Pathol 68(3): 241-245.

11. Riley RS, Hogan TF, Pavot DR, Forysthe R, Massey D, et al. (2004) A pathologist's perspective on bone marrow aspiration and biopsy: I. Performing a bone marrow examination. J Clin Lab Anal 18(2): 70-90.