

Bone marrow examination

Indications and diagnostic value

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ABSTRACT

Objectives: To identify the main indications for bone marrow examination in a University hospital setup and the most common diagnoses encountered. To also identify the extent of correlation, if any, between the preliminary diagnosis and the result of the final bone marrow diagnosis.

Methods: The requests and reports of all bone marrow biopsies and aspirations carried out during a 12-year period from January 1988 through to December 1999, in King Fahd Hospital of the University, Al Khobar, Kingdom of Saudi Arabia were retrospectively reviewed. The information extracted included the main indications for performing this procedure, age groups involved, and the most common diagnoses encountered. A specially designed form was used for this purpose and the data was analyzed using the statistical package for social sciences. Randomly selected slides of the most common diagnoses were reviewed to concur with the diagnosis.

Results: There was a total of 1813 bone marrow biopsies or aspirations, or both, performed. The main indications for bone marrow examination in a descending order of frequency were the following: The diagnosis and management of acute leukemia 403 (22.2%), staging for

lymphoma 276 (15.2%), evaluation of pancytopenia 215 (11.9%), thrombocytopenia 173 (9.5%), investigation of anemia 151 (8.3%), fever (pyrexia of unknown origin) 130 (7.2%), lymphadenopathy 120 (6.6%), and hepatosplenomegaly 80 (4.4%). The most common diagnoses encountered were: acute lymphoblastic leukemia 242 (13.3%), immune thrombocytopenia 123 (6.8%), acute myeloblastic leukemia 80 (4.4%), hypersplenism 79 (4.4%), chronic granulocytic leukemia 73 (4.0%), megaloblastic anemia 66 (3.6%), bone marrow positive for lymphomatous infiltration 63 (3.5%), chronic lymphocytic leukemia 40 (2.2%), and multiple myeloma 32 (1.8%).

Conclusion: This study confirms that bone marrow examination is a very important investigation for establishing the diagnosis in many conditions, especially hematological neoplasms. The most common indication for this procedure in our hospital was to confirm and manage acute leukaemia and the most common diagnosis was acute lymphoblastic leukemia.

Keywords: Bone marrow examination, indications, diagnosis, University hospital.

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Bone marrow examination is a very important investigation for the diagnosis of many hematological and non-hematological diseases. It may also be necessary in the evaluation of a number of disease processes, and may have an important role in establishing the final diagnosis. Bone marrow

sampling is the process of obtaining marrow tissue for laboratory analysis and diagnosis. The history of bone marrow examination goes back to 1908, when Ghedini of Genoa¹ performed the first biopsy. In the first few decades thereafter the reports were based on smears of bone marrow aspiration, but Peabody² in

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1927 reported the results of sections of curetted tibial marrow. In 1933 Custer³ reported an account of his experience with biopsy of sternal marrow, and he demonstrated the importance of histological sections and touch preparations of marrow compared with smears alone.

In the last 40 years, bone marrow trephine biopsy has become popular due to the availability of relatively simple biopsy needles. During the late 1950s McFarland and Dameshek introduced a means of obtaining bone marrow core biopsies to overcome the problems of a dry tap or when insufficient material was obtained during aspiration.⁴ It soon became clear that trephine biopsy could provide valuable information in many types of bone marrow diseases like leukemias, lymphoproliferative and myeloproliferative disorders, metastases, myelodysplasia and reactive disorders. The absolute indications for bone marrow examination include evaluation of leucopenia, anemia, pancytopenia, leucoerythroblastosis and diagnosis of leukemia as well as monitoring the effects of therapy.^{5,6} Relative indications include evaluation of iron metabolism, unexplained fever (PUO) or splenomegaly, and sampling for chromosomal analysis, immunophenotyping, or microbiological cultures.^{5,6} Since the 1980's, bone marrow examination has been found to be of diagnostic utility in human immunodeficiency virus (HIV) patients.⁷ The preferred sites for marrow aspiration, and biopsy in adults or children or both, include posterior superior iliac spine, anterior superior iliac spine, iliac crest, sternum and vertebral spinous processes. The tibia is the preferred site for infants below 18 months of age.^{5,6,8}

Contraindications to bone marrow aspiration/biopsy include hemophilia and other major disorders of coagulation which constitute an absolute contraindication.^{5,8,9} Thrombocytopenia, however severe, is no contraindication, and to prevent excessive bleeding pressure is applied on the site firmly for 5-10 minutes.^{5,7,8,9} Other reported contraindications include skin infection, osteomyelitis, previous radiation therapy in the area of sampling and an uncooperative patient.⁶ Reported complications include cardiac tamponade, myocardial or aortic lacerations, bone marrow embolization to the lung (in sternal perforation), perforation of iliac bone with retroperitoneal hemorrhage in patients with osteoporosis, infection, hemorrhage or pain at site of aspiration/biopsy⁵⁻⁸ and a rare report of plasmacytoma in muscle as a result of needle tract seeding after percutaneous bone marrow biopsy in a case of multiple myeloma.¹⁰ The procedure is usually safe, and if carried out with expert and skilful manipulation on the part of the physician it is usually tolerated with hardly any complications. Premedication and sedation are

helpful measures before bone marrow biopsy, especially in children.^{11,12} The procedure is usually performed by an adult or pediatric hematologist/oncologist as technical expertise is needed to obtain adequate samples, arrange for special stains, immunophenotyping and cytogenetic studies. In our institution bone marrows are also performed by residents in clinical pathology, pediatrics and internal medicine. The main aims of this retrospective study were to identify the main indications for this procedure and the common diagnoses encountered in a university hospital and to discuss some issues concerning bone marrow examination in general.

Methods. The bone marrow records from the hematology/pathology sections of the Clinical Laboratories of King Fahd Hospital of the University (KFHU) Al-Khobar, KSA during the period from January 1988 through to December 1999 were reviewed. A specially designed form was used for this purpose which included information on age, sex, nationality, indication for bone marrow, symptoms, preliminary diagnosis, microscopic description, site, whether bone marrow sampling was unilateral or bilateral, inadequate or adequate, and final diagnosis. The forms were completed by abstracting any other relevant information from the medical records of these patients. The specimens received from adults (age >14 years) included both bone marrow biopsy and aspiration except in occasional cases where only one was obtained such as a dry tap or where biopsy could not be taken. In children, it was mostly only bone marrow aspiration except in very rare cases where aplastic anemia or metastases were expected or an aspiration could not be obtained. Bone marrow smears are stained routinely with Wright-Giemsa stain and Perl's, while sections are stained routinely with Hematoxylin and Eosin (H & E), Perl's (iron) and reticulin. For certain indications, to confirm the diagnosis, special stains are used; for example periodic acid Schiff (PAS), Sudan black, double esterase, acid phosphatase, amyloid, fungus, trichrome, immunoperoxidase, Ziehl-Neelsen, immunohistochemical stains and others as needed. Randomly selected slides of some of the most common diagnoses were reviewed. Data were entered using a d-Base program, and analyzed using PC-statistical package for social science version 7.0 software.¹³ Statistical analysis included descriptive statistics, bivariate analysis such as t-test, Chi-square and analysis of variance (ANOVA), were used as appropriate. The level of significance was set at <0.05.

Results. *Age and sex distribution.* There were a total of 1813 bone marrow examinations carried out during the study period. There were 836 samples

Table 1 - Most common indications for bone marrow examination, King Fahd Hospital of the University, Al-Khobar, January 1998 through to December 1999.

Indication	N (%)
In diagnosis and management of acute leukemia	403 (22.2)
Staging for lymphoma	276 (15.2)
Evaluation of Pancytopenia	215 (11.9)
Thrombocytopenia	173 (9.5)
Anemia	151 (8.3)
Fever	130 (7.2)
Lymphadenopathy	120 (6.6)
Hepatosplenomegaly	80 (4.4)
Exclude metastasis/malignancy	60 (3.3)
Exclude blastic transformation of CGL	40 (2.2)
Hepatomegaly	37 (2)
Miscellaneous	128 (7.1)
Total	1813 (100)
N=number, CGL=chronic granulocytic leukemia	

Table 2 - The most common diagnoses encountered in King Fahd Hospital of the University, Al-Khobar, January 1988 through to December 1999.

Diagnosis	N (%)
Acute lymphoblastic leukemia	242 (13.3)
Immune Thrombocytopenia	123 (6.8)
Hypocellular bone marrow (due to different causes)	105 (5.8)
Acute myeloblastic leukemia	80 (4.4)
Hypersplenism	79 (4.4)
Chronic granulocytic leukemia	73 (4)
Megaloblastic anemia	66 (3.6)
Lymphoma (bone marrow positive)	63 (3.5)
Chronic lymphocytic leukemia	40 (2.2)
Multiple myeloma	32 (1.8)
Myelodysplastic syndrome	24 (1.5)
Miscellaneous diagnoses	192 (10.6)
Normal bone marrows	694 (38.3)
Total	1813 (100)
N=number	

from children and 977 from adults. The mean age was 24.04 ± 22.3 years, (median = 15). The youngest patient was 4 days and the oldest patient 100 years. The mean age for adults was 40.6 ± 17.8 years, while that for children was 4.9 ± 3 years. The male to female ratio was 1.6:1.

Indications and diagnoses. The most common indications for bone marrow examination in descending order of frequency are summarized in **Table 1**. In children (≤ 14 years) we found that the main indications for bone marrow examination were in descending order of frequency: diagnosis and management of acute leukemia 275 (32.9%), fever 130 (15.6%) hepatosplenomegaly 100 (12%), isolated thrombocytopenia 92 (11%), pancytopenia 82 (9.8%) lymphadenopathy 68 (8.1%), anemia 55 (6.6%), and miscellaneous indications like staging for lymphomas, excluding metastasis, mediastinal, abdominal or renal masses, leucopenia, hypersplenism, leucocytosis and neutropenia 34 (4.1%). The most common diagnoses encountered are summarized in **Table 2**. In more than 38% of the marrows no pathology was found.

Signs, symptoms and findings. The most common signs or symptoms that patients presented with included: Fever 219 (12.1%), symptoms of anemia and pallor 180 (9.9%), mucocutaneous

bleeding 141 (7.8%), lymphadenopathy 137 (7.6%), signs and symptoms of pancytopenia 136 (7.5%), bone pain 60 (3.3%), generalized weakness 70 (3.9%), weight loss 58 (3.2%), mediastinal, abdominal, paraspinal, or renal masses in 55 (3.1%) of patients.

Site of bone marrow examination. The bone marrow sample was obtained from the anterior superior iliac spine (35%) of specimens, or posterior superior iliac spine (64%) with either Islam or Jamshidi bone marrow needles and very rarely in exceptional cases sternal aspirations (0.2%).

Unilateral versus bilateral bone marrows. Of the 276 samples taken for staging of lymphoma 70 (25.3%) of these cases were taken bilaterally, and 206 (74.7%) were carried out unilaterally. Sixty (21.7%) of the cases, were positive for lymphoma, while in 216 (78.3%) of the cases it was negative for lymphoma. In those cases where bone marrow was found infiltrated by lymphoma tissue, 50 were carried out unilaterally and 10 bilaterally.

Adequacy of bone marrow samples. In 175 (9.7%) of bone marrow specimens, the samples were reported as "inadequate", or "unsuitable for reporting" and this was either due to a diluted inadequate bone marrow aspiration or an inadequate bone marrow biopsy where most of the specimen was

cortical bone or a crushed bone marrow specimen. One hundred and fifteen (65.7%) of these specimens were of pediatric bone marrows, where the sample was often blood diluted. The remaining 60 (34.3%) were from adult bone marrow specimens.

Clot samples. Bone marrow clots were submitted in 60 (3.3%), of the samples, in addition to biopsy and aspiration, and 30 (50%) provided information similar to bone marrow aspiration and biopsy. They occasionally were informative in cases where biopsies or aspirations were inadequate.

Preliminary diagnosis and final diagnosis. When the preliminary diagnosis, as suggested by treating physicians on the basis of clinical and laboratory information, was compared with final diagnosis the results were significant (p value $< .0001$). In other words, in most of the cases, the expected diagnosis was correct especially for cases of acute and chronic leukemias. While for the final diagnoses of fibrosis (secondary), hypercellularity, bone marrow aplasia, myelodysplastic syndrome erythroid hyperplasia, and combined deficiency anemias there was less agreement between preliminary diagnosis and final diagnosis.

Discussion. The main objective of this retrospective study was to identify the major indications for which clinicians order bone marrow biopsies and aspirations in a university referral hospital. In this study, the most common encountered diagnosis was acute lymphoblastic leukemia, a common malignancy in both children and adults in the KSA.¹⁴⁻¹⁸ Coincidentally the diagnosis and management of acute leukemias was also the most common indication for bone marrow examination in both adults and children. Isolated thrombocytopenia was also a common indication for bone marrow examination especially in children, where it was mostly due to an immune thrombocytopenia. There has been some controversy regarding the need and justification of bone marrow examination in acute childhood idiopathic thrombocytopenic purpura (ITP) or an isolated thrombocytopenia. In these reports the findings of the authors provide some evidence for the low yield and probable lack of significant benefit of bone marrow aspiration in the setting of typical acute childhood ITP.^{19,20,21} However, a survey of 322 pediatric hematologists revealed that 74% would perform a bone marrow examination in acute childhood ITP, and the foremost reason cited was the need to exclude leukemia, dysmyelopoietic syndromes and aplastic anemia.²¹ It was suggested that bone marrow examination could be limited to those patients with atypical features of ITP both clinically and hematologically or those patients being treated with corticosteroids,¹⁹ and that if there is significant bone

marrow pathology associated with thrombocytopenia, additional abnormalities in the peripheral blood would often be apparent.^{20,21} In our institution, however, all cases of isolated thrombocytopenia are subjected to bone marrow examination, to exclude any other diagnostic possibilities, even if clinical and laboratory data suggest peripheral destruction, to avoid the risk of obscuring the diagnosis especially after treatment.

In this study another common diagnosis and indication for bone marrow examination was in staging for lymphomas, another common malignancy in the KSA.¹⁵⁻¹⁸ Bone marrow examination is routinely carried out during staging of patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD). Bone marrow involvement denotes stage IV disease. Finding malignant lymphoma in the marrow is dependent on obtaining adequate biopsy material.²² The optimal examination of the bone marrow includes study of trephine biopsy sections, trephine imprints, aspiration smears and peripheral blood smears. Trephine biopsy sections generally provide the most useful information in the assessment of HD or NHL. However, in some cases of NHL the aspirate smears have been positive for malignancy when sections are negative.²² In patients with HD, aspiration smears rarely show evidence of involvement even when trephine biopsy sections show extensive marrow involvement.²² Many lymphomas infiltrate the bone marrow in a focal pattern of distribution, and the lesions may be missed if the volume of biopsy is inadequate. It is known that performing bilateral iliac crest marrow biopsies increases the yield of marrow involvement, as specimen size is theoretically doubled and tissue is provided from 2 separate sites.²²

In one study, where the length of biopsy specimen was correlated with yield of detection, it was found that a generous bone marrow biopsy sample is recommended, (>0.5 cm), but a very lengthy one (>2.5 cm) does not significantly increase yield of detection.²³ In this study, bilateral bone marrows did not appear to increase the yield of detection of lymphomatous tissue, as even when they were carried out unilaterally there was evident lymphomatous involvement. It has been stated also that the value of bilateral bone marrow trephines in staging procedures is limited and is only indicated in a selected group of patients.²⁴

Another encountered indication for bone marrow examination was to exclude malignancy in patients with unexplained weight loss and PUO. In occasional cases bone marrow was positive for lymphoma or metastasis. Another important indication for bone marrow sampling is staging of solid tumors and detection of occult metastasis, especially neuroblastoma in children, and other tumors in adults like breast, prostate, lung etc. Immunohistochemistry of the bone marrow, has a very important role also in

the diagnosis of these and many other diseases. In children neuroblastoma is the 2nd most common cause of bone marrow infiltration after ALL.²⁴ In this study 20 cases of neuroblastoma were encountered and in 9 cases (45%), bone marrow involvement was diagnosed by aspiration. No trephine biopsies were carried out in these infants. However, some studies have emphasized the higher yield of detection of metastatic neuroblastoma by bone marrow biopsy,²⁵ and the authors recommended that even with immunohistochemistry, both biopsy and aspiration should be performed to have the highest yield of detection in bone marrows. Another less common indication we encountered was tuberculosis (TB), brucellosis or leishmaniasis especially in the common indication category of PUO. In 5 specimens, TB was diagnosed from bone marrow biopsies or clot, or both, and where granulomas were recognized.²⁴ Twelve cases of leishmaniasis were diagnosed, in some of the patients with pancytopenia, fever or hepatosplenomegaly. In the context of exclusion of TB, brucellosis, or an infectious etiology for patients with PUO and organomegaly, bone marrow is also aspirated for various microbiological cultures and stains, which aid in the diagnosis.

Investigation of anemia, the 5th most frequent indication, showed various causes. The most common in this study was megaloblastic anemia. Other causes for anemia diagnosed included anemia of chronic disease, iron deficiency anemia, hemolytic anemias, aplastic anemia and myelodysplastic syndrome (MDS). A very common diagnosis and interpretation encountered also, was bone marrow hypoplasia (5.8%). The causes of this were so diverse, especially post-chemotherapy induced hypocellularity, commonly seen in cases of leukemia and lymphoma. De novo marrow hypoplasia or aplasia (aplastic anemia) was less common however.

The indications for bone marrow examination in this study were almost similar to another study from the KSA,²⁶ where the most frequent indications for this procedure were evaluation of postchemotherapy bone marrow in acute leukemias (26.2%), followed by suspected infiltration by lymphoma or carcinoma (10.3%), and thrombocytopenia (9.9%). Although the frequencies of acute leukemia (27.3%), malignant lymphoma (13.3%), chronic granulocytic leukemia (7%), chronic lymphocytic leukemia (3.8%) and myelodysplastic syndrome (2.3%), were relatively similar in being common diagnoses, there were marked differences in the frequency of multiple myeloma (8.3%), and the nonleukemic myeloproliferative disorders (MPD) (9.4%). In our study multiple myeloma was diagnosed in 1.8% of the cases and MPD in 1%. The causes for these differences may be many including the size of the hospital, nationalities, age groups involved, and the

higher number of bone marrow specimens analyzed.

In 9.7% of the bone marrow specimens, the sample was inadequate. The inadequacy was either in the form of a highly blood diluted bone marrow aspiration, especially common in children (65.5% of pediatric bone marrows were in that category) or a crushed or inadequate bone marrow biopsy specimen or both, where it was mostly cartilage (58.3% of inadequate trephine adult samples were in that category). In recent studies in which the aim was to evaluate the success in obtaining adequate biopsy cores from children, they found that in 13 centers submitting cores, failure rates ranged from 2.6% to 50%.²⁷ They suggested that those centers with high failure rates should review their practice and make attempts to improve adequacy of biopsy cores. They also suggested increasing the proportion of biopsies performed by hematologists, to reduce the rate of unsuccessful operations. The cause of inadequacy of specimens in this study, was mostly due to lack of experience of the physicians performing the procedure. In the study by Al-Gawaiz²⁶ from KSA, out of 3494 bone marrow samples, 160 (4.5%) were inadequate for evaluation. In some bone marrow procedures, a specimen of bone marrow clot was also submitted along with the biopsy for processing. The clot was informative in 5 cases where the diagnoses were, ITP, multiple myeloma, TB, hypocellular marrow and a normal marrow. In a recent short report, clot sections from neonates provided information on marrow cellularity and megakaryocyte numbers comparable to those obtained from a biopsy.²⁸ It can be recommended that any excess clotted bone marrow aspiration be also submitted for processing, particularly if the sample is hemodiluted.

When the preliminary diagnosis as suggested by treating physicians was compared to final diagnostic interpretations, the diagnosis was correct in most of the cases. This was especially significant in cases where acute and chronic leukemias were suspected.

In conclusion, bone marrow evaluation is a very important aid in diagnosis and management of hematological disorders. Evaluation of bone marrows in acute leukemia followed by staging for lymphoma were the most frequent indications in this study. The most common diagnoses were acute lymphoblastic leukemia and immune thrombocytopenia.

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