



Original Research Article

Results of Bone Marrow Examination Over 9 Years Period in Iraqi Patients from Babil Province

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Abstract

The aim of this study is to assess the results of bone marrow aspiration with or without trephine biopsy in Babil province.

In this observational study, 5644 Iraqi patients were included, male: female ratio was 1.3:1 and age range was 1-78 years. The patients attended hospital for bone marrow aspiration with or without biopsy over a period of 9 years from 1st March 2006 till 1st March 2015. Pallor and anemia (55.3 %) were the most common indication. The morphological examination of blood film and bone marrow were performed.

The final diagnosis was reached in 93.21% (5261/5644) of patients by morphological examination of bone marrow samples only. However, other 383 (6.78%) of patients needed further advanced tests. The result of BME was normal in 28.72% (1621/5644) of patients which was the most common result.

Non-Hodgkin's lymphoma was the cause of bone lytic lesions in a significant number of cases and it should be kept in mind.

This study concluded that bone marrow examination is a worthy test and can reach the diagnosis in majority of cases with morphological examination only, and this ratio can be increased by introduction of other supplementary tests like CD markers and immunohistochemistry. Normal results also helped diagnosis by their exclusive value. Doctors must be encouraged to request BME whenever they found it indicated.

Key words: Bone marrow examination, Aspiration, biopsy, Non-Hodgkin's lymphoma .

نتائج فحص نخاع العظم خلال فترة تسعة سنوات للمرضى العراقيين من محافظة بابل

الخلاصة

يعتبر فحص نخاع العظم من الفحوصات المهمة لتشخيص أو إستثناء العديد من الأمراض التي تصيب نخاع العظم نفسه أو أجزاء أخرى من جسم الانسان. إن الهدف من هذه الدراسة هو تقييم نتائج فحوصات نخاع العظم التي أجريت في محافظة بابل خلال فترة تسعة سنوات تمتد من الأول من آذار ٢٠٠٦ ولغاية الأول من آذار ٢٠١٥ وتبين إجراء ٥٦٤٤ فحص سحب نخاع عظم مع خزعة النخاع أو بدونها. كانت نسبة المرضى الذكور الى الاناث هي ١:١,٣ والأعمار تتراوح بين سنة واحدة و ٧٨ سنة. كان المرضى يراجعون المستشفى لعدة أسباب أهمها فقر الدم والشحوب (٥٥,٣%).

تم إجراء فحص صورة الدم ونخاع العظم لكافة المرضى والتوصل الى التشخيص النهائي في ٩٣,٢١% (٥٢٦١/٥٦٤٤) من الحالات بإستخدام فحص الهيئة فقط, بينما إحتاج باقي المرضى (٣٨٣/٥٦٤٤) إلى فحوصات متقدمة أخرى للوصول إلى التشخيص النهائي. كانت نتيجة فحص نخاع العظم طبيعية في ٢٨,٧٢% (١٦٢١/٥٦٤٤) من المرضى والذين شكلوا النسبة الأكبر من النتائج في عينة المرضى الداخلة في هذه الدراسة. لقد شكل مرض المفوم اللاهوجكيني نسبة مهمة من التشخيص النهائي لحالات تحلل العظم المرضي لذا يجب أن يبقى هذا الاحتمال في البال عند محاولة تشخيص حالات مشابهة.

توصلت هذه الدراسة إلى أن فحص نخاع العظم هو من الفحوصات المهمة في تشخيص الكثير من الأمراض وإستخدام فحص الهيئة فقط, وبالامكان زيادة هذه النسبة بإستخدام الفحوصات الحديثة والمتطورة في بعض الحالات الصعبة. كما إن تشخيص نخاع العظم على أنه طبيعي

مفيد أيضا باستثناء بعض الحالات المرضية. نوصي بتشجيع الأطباء على الاستفادة من هذا الفحص وعدم التردد من طلبه عند الحاجة له كونه فحص غير خطر ورخيص التكلفة.

الكلمات المفتاحية : فحص نخاع العظم، سحب نخاع العظم، خزعة، اللمفوم اللاهوجيكي.

Introduction

Bone marrow examination was first applied to clinical evaluation in 1905, when the Italian physician Pianese reported bone marrow infiltration by the parasite Leishmania [1].

Currently, inspection of bone marrow is considered one of the most valuable diagnostic tools for evaluating hematologic disorders [2]. Indications have included diagnosis, staging, and therapeutic monitoring for lymphoproliferative disorders (such as chronic lymphocytic leukemia and lymphoma), myeloproliferative disorders, myelodysplastic syndrome and multiple myeloma. In addition, evaluation of cytopenia and leukocytosis can be performed [3].

The Use of bone marrow examination has grown to include other, nonhematologic, conditions like, for example, in the investigation for fever of unknown origin (FUO), specifically in patients with autoimmune deficiency syndrome (AIDS) [4].

In addition, the diagnosis of storage diseases (eg. Niemann-Pick disease and Gaucher disease) [5] and the assessment for metastatic carcinoma and granulomatous diseases (eg, sarcoidosis) can be performed.

Bone marrow analysis can also be done in patients with idiopathic thrombocytopenia purpura (ITP), incidental elevated serum paraprotein levels, iron deficiency anemia and iron status, polycythemia vera, essential thrombocytosis, or infectious mononucleosis; but these conditions are often more appropriately diagnosed by routine laboratory evaluation [6].

Sampling of the marrow consists of aspiration of the cellular component, tissue biopsy, or both. Aspiration of the marrow has been primarily utilized for cytologic

assessment, with analysis directed toward assessing the morphology and obtaining a differential cell count. Further sampling allows material to be directed toward other ancillary tests, such as cytogenetics, molecular studies, microbiologic cultures, immunohistochemistry, and flow cytometry. While biopsies allow evaluation of the marrow's overall cellularity, detection of focal lesions, and determination of the extent of infiltration by various pathologic entities [7-9].

Aspiration sampling is usually performed before biopsy. The reason is that the biopsy technique increases thromboplastic substances which leads to a reduction in the effectiveness of an aspiration sampling.[8,10,11]

Controversy exists about bilateral iliac biopsies. However, some studies have found that this technique increases the probability of detecting focal lesions like carcinoma and lymphoma staging, where 11-16% of cases may be missed with unilateral biopsies [12].

The aim of this study is to assess the results of BME (aspiration with or without biopsy) in Babil province, to assess the importance of BME in confirming some pathologies or excluding others, and to assess to what extent that morphological BME only is enough to reach definite diagnosis.

Materials and Methods

This is an observational study included 5644 Iraqi patients from Babil province in the middle of Iraq 100 Km south of Baghdad. 56.9% (3212/5644) of them were males and 43.1% (2432/5644) were females. The patient's age ranged from 1-78 years with maximum number in age group from 20 – 60 years and mean age was 38.8 years.

The patients attended Merjan Teaching Hospital, Al-Hilla Teaching Hospital or a private laboratory for multiple complaints

requiring bone marrow examination (BME). They represented almost all cases who had done BME in Babil over a period of 9 years from 1st March 2006 till 1st March 2015. For all patients, a relevant medical history and physical examination were done by a consultant physician, then blood samples were taken for blood smear examination, while bone marrow samples were collected either aspiration alone as in 77.73% (4387/5644) of cases or aspiration and biopsy as in 22.27% (1257/5644) of them. Other supplementary blood test were performed according to need e.g. blood sugar, renal function, ferritin, B12, folate...etc and some relevant radiological investigations were done. No additional tests (like special stains or CD markers) were performed on the bone marrow samples except for some suspicious cases who could offer for the cost as they weren't available for free in Babil hospitals.

Bone marrow was aspirated with or without biopsy (according to physician's request) from posterior superior iliac crest under local anesthesia (2-3 ml of

lidocaine). The aspiration samples were stained with standard stains used for the initial evaluation include Wright and May-Grunwald-Giemsa stains, which enhance cytologic detail, while biopsy samples were processed, stained with H and E stain [13,14] and examined. The morphological examination of blood film and bone marrow were performed by an expert hematologist using Olympus CX20 light microscope.

The indications and type of BME were documented, the results were followed and any additional tests performed were checked. Statistical analysis was done using descriptive statistics (the mean and median).

Results

A total of 5644 Iraqi patients were enrolled in the study. Male: female ratio was 1.3:1 and mean age was 38.8 years. The age distribution of the patients was demonstrated in table (1). Most of the patients 69.93% (3947/5644) were aged 20-60 years.

Table 1: Age distribution of study group

Age range	< 20 years	20-40 years	40 – 60 years	> 60 years
No. of patients	899	1914	2033	798
%	15.92	33.91	36.02	14.13

Indications for requesting BME were shown in table (2). The patient might have more than one indication e.g. anemia, thrombocytopenia and splenomegally.

The final diagnosis was reached in 93.21% (5261/5644) of patients by morphological examination of bone marrow samples only. However, other 6.79% (383/5644) of patients had abnormal marrow and definite diagnosis needed further advanced investigations to be performed on bone marrow samples. We had enforced to send those patients to hematological centers in Baghdad or abroad in Jordan, Lebanon or India for further assessment. 174 of them

Pallor and anemia (55.3 %) were the most common indication for BME in this study followed by leukocytosis (51.26 %) and bleeding tendency (35.28 %).

couldn't of or for the cost and continued to be undiagnosed. In others 209 (%); further tests were done and final diagnosis was reached in 183 (88 %) of them; but remained obscure in 26 patients. So by the end of this study, we had 200 cases without definite diagnosis.

The result of BME was normal in 28.72% (1621/5644) of patients which was the most common result. The 5 most common diseases diagnosed were acute

myeloblastic leukemia (12.76 %), acute lymphoblastic leukemia (10.95 %), multiple myeloma (8.65 %), chronic

lymphocytic leukemia (7.32 %) and immune thrombocytopenic purpura (6.72 %). Table (3)

Table 2: The indications for requesting BME in the study group.

The indication	No. of patients	%
Pallor / anemia	3121	55.3
Polycythemia	185	3.28
Leukopenia	982	17.4
Leukocytosis	2893	51.26
Thrombocytopenia	1004	17.79
Thrombocytosis	109	1.93
Abnormal cells in blood film	1273	22.56
Fever / FUO	1087	19.26
Bleeding tendency	1991	35.28
High ESR	898	15.91
Organomegally	1065	18.87
Lymphadenopathy (Splenomegally and/or hepatomegally)	732	12.97
Follow up for remission (Leukemia, lymphoma ...etc.)	911	16.14
Assess marrow involvement (Lymphoma, solid tumors)	776	13.75
Bone pain / Lytic lesion pathological fracture	384	6.8
Others	364	6.45

Table 3: Final results of bone marrow examination in the study group.

Diagnosis	No. of patients	%
Normal	1621	28.72
Acute myeloblastic leukemia (AML)	720	12.76
Acute lymphoblastic leukemia (ALL)	618	10.95
Multiple myeloma (MM)	488	8.65
Chronic lymphocytic leukemia (CLL)	413	7.32
Immune thrombocytopenic purpura (ITP)	379	6.72
Chronic myelocytic leukemia	Chronic phase	194
	Accelerated	21
		4.38

	Blastic crisis	32	
Kala azar		178	3.15
Myelofibrosis		155	2.75
Aplastic anemia (Including pure red cell aplasia)		141	2.5
Polycythemia rubra vera (PRV)		99	1.75
Combined deficiency anemia		91	1.61
Secondary metastasis to bone marrow		91	1.61
Myeloproliferative neoplasia (MPN)		73	1.29
Undifferentiated leukemia		65	1.15
Myelodysplastic syndrome (MDS)		64	1.13
Non-Hodgkin's lymphoma (NHL)		60	1.06
Megaloblastic anemia		41	0.73
Hypersplenism		37	0.66
Hairy cell leukemia (HCL)		21	0.37
Others		42	0.74

Normal BME results had included those who were previously diagnosed with malignancy (e.g. acute or chronic leukemia, multiple myeloma of lymphoma) and BME was done as follow up test and showed remission. On the other hand, cases of leukemia relapse were excluded from results if the patient was previously included in the study at the time of his/her initial diagnosis.

Other less common diagnoses included multiple types of anemia (iron deficiency, anemia of chronic disease and hemolytic anemia) in 20 patients, Essential thrombocytosis in 9 patients, Gaucher's disease in 8 patients and Neiman-Pick disease in 5 patients.

Bony lytic lesions were the indication for BME in 384 patients. The result was normal in 16.4% (63/384), multiple myeloma in 72.6% (279/384) and secondary metastasis to bone marrow in 8.9% (34/384). The remaining 2.1% (8/384) was diagnosed with non-Hodgkin's lymphoma (NHL).

Discussion

In this study, 5644 Iraqi patients were included over a period of 9 years. Bone

marrow examination (BME) was indicated in all of them, whether to confirm or exclude a disease.

To the extent of my knowledge and my internet search, no similar study is present. I didn't find any previous study describing the ratio of different diagnoses of BME or the percentage of different indications of BME.

More than 28 % of results in the recent study were normal. These normal results might have a significant exclusive importance, however, requesting a non-indicated BME may be a possible cause.

Normal bone marrow result is as important as diseased one. Hence, this large ratio of normal results mustn't be against requesting bone marrow test when indicated, especially if safety of the procedure is taken in consideration.

In 2002 the British Society of Haematology initiated an annual survey to assess the various types and incidence of bone marrow biopsy adverse events.[15] Bain summarized results of a 7-year (1995-2001) retrospective study and identified 26 adverse events among approximately 54,890 biopsies, with an

overall annual incidence of 0.05%. The most common side effects, in order of decreasing frequency, were hemorrhage, needle breakage and infections.

Risk factors for hemorrhage included concurrent anticoagulation or platelet dysfunction. Two cases were fatal and were attributed to sepsis and massive hemorrhage [15].

Four years later, a prospective study by Bain revealed 15 adverse events in a single year, with an overall incidence of 0.07% [11]. However, although hemorrhage was still considered the most commonly encountered side effect, this study revealed that pain, anaphylactic reaction, and fractures were prominent secondary consequences. Two fatalities, attributed to laceration of blood vessels, were reported from 20,323 bone marrow aspiration and biopsy procedures [11].

In this study, non-Hodgkin's lymphoma was an important cause of bone lytic lesions 2.1% (8/384) and should be kept in mind as a possible cause for this lesion; however, multiple myeloma was still the most common cause. Normal bone marrow (16.4%) in patients with lytic lesion was more common than secondary metastasis to marrow (8.9%). Most common sites of primary malignancy were breast and gastro-intestinal tumors.

Ehara et al found that bone osteolysis in patients with adult T-cell leukemia-lymphoma (ATLL) is a paraneoplastic feature and caused by parathyroid hormone-related peptides (PTHrP) [16]. While in the recent study, it was found that bone lytic lesions were from direct marrow invasion by lymphoma cells. No one of cases was resulted from direct leukemic cells invasion.

B-cell lymphomas rarely present with lytic bone lesions, [17,18] and primary bone lymphoma is very rare and it's diagnosis is based on a histopathological examination and imaging studies. Lymphomas are most often found in the axial skeleton, pelvis, femur and humerus. Guzki found that just 0.38% (5/1327) of patients with bone tumors were diagnosed as a case of lymphoma [19].

B-cell type represents 10-20% of lymphoblastic lymphomas [20]. It predominantly presents with extranodal masses especially in the skin and less commonly in the bone [21,22]. Bony lesions are usually osteolytic, although few cases with osteoblastic lesions have been reported [23].

Conclusion

Bone marrow examination is a worthy test as it gave the final diagnosis in this study for more than 93 % of cases with morphological examination only. Normal results also helped diagnosis by their exclusive role for some pathologies. Additional diagnostic or confirmatory tests may be needed in minority of cases.

Doctors must be encouraged to request BME whenever they found it indicated whether to diagnose a disease or to exclude another as BME is generally a safe procedure.

Non-Hodgkin's lymphoma is an important cause of bone lytic lesions and may need a high index of suspicion to be diagnosed.

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