Bone marrow trephine in some hematological and non-hematological disorders

Mohammed S. Saeed*, Nazar M. Jawhar**
***Department of Pathology, College of Medicine; ** Department of Pathology, Nineveh College of Medicine, University of Mosul.**

(Ann. Coll. Med. Mosul 2010; 36 (1 & 2): 63-71).
Received: 11th Nov 2009; Accepted: 19th May 2010.

ABSTRACT

Objective: To evaluate the frequency, age distribution and document the histological pattern of various hematological disorders reported in bone marrow biopsy.
Methods: A retro and prospective study carried out from 2000 to 2007 at pathology laboratory of Irbil Razkary Hospital. A total number of 117 cases were investigated. The biopsy was taken from posterior superior iliac spine by the clinician. A length of 0.5 to 2 cm of marrow element was obtained, put overnight in 10% formalin for fixation, followed by decalcification in 5% nitric acid. Then processed in usual manner. Sections were examined by 2 pathologists independently.
Results: the mean age of patients was 46.16 years ranging from 2 years to 76 years. The male to female ratio was 1.49:1. The commonest presenting clinical features of patients underwent bone marrow biopsy were pallor (91.4%), followed by body weakness (59.0%). The most frequent histological diagnoses in order of frequency were unremarkable bone marrow (28.20%), lymphoma (11.1%), acute leukemia, chronic myeloproliferative disorders (9.40%), chronic leukemia, (5.12%), multiple myeloma (3.42%), metastatic tumor (2.56%), myelodysplastic syndrome and megaloblastic anemia equally reported (1.71%), pure red cell aplasia and granulomatous inflammation were present in (0.85%).
Acute leukemia was encountered mostly in 1st and 2nd decades of life. Lymphoma, chronic leukemia, chronic myeloproliferative disorders occur in 4th and 5th decades. Myelodysplastic syndrome presented in older age group 5th and 6th decades. Multiple myeloma and metastases were seen in 6th and 7th decades of life. Other disorders were randomly distributed.
Conclusion: Bone marrow trephine biopsy is an invasive procedure with few known complications, but is a valuable diagnostic tool in the diagnosis, staging, management and follow up of various conditions both neoplastic and non-neoplastic. High percentage of cases in our study showed normal marrow finding, this may reflect overindication of marrow biopsy, such finding urge for more clinicopathological coordination and data analysis.

Keywords: Bone marrow trephine biopsy, lymphoma, leukemia, myeloproliferative disorders, myelodysplastic syndrome, multiple myeloma.

الخلاصة

الأهداف: لغرض تقييم التردد وتوزيع الأعمار وتثبيت النمط النسيجي لاضطرابات الدم المختلفة مع موجودات خزع نخاع العظم.
الطرق: أجريت دراسة راجعة ومستقبلية للفترة من سنة ٢٠٠٠ ولغاية ٢٠٠٧ في مختبر الإمراض – مستشفى رازكاري في اربيل. ولقد تم فحص ١١٧ حالة وقد أخذت الخزع من شوكة الحرقفة الخلفية العلوية من قبل الطبيب ألسريري. ولقد تم الحصول على ٠,٥ إلى ٢ سم طولا من مادة النخاع ووضعت في ١٠% فورما لين للتثبيت ثم اتبعت بإزالة الكلس بمادة

٥% حامض النتريك ومن ثم مررت بالطريقة الاعتيادية. ولقد تم فحص المقاطع النسيجية من قبل اثنان من اختصاصي علم الإمراض وبصورة مستقلة.

النتائج: لقد كان المتوسط العمري للمرضى ٤٦,١٦ سنة وبتراوح بين ٢-٧٦ سنة. وكانت نسبة الذكور إلى الإناث ١,٤٩:١. إن الإمراض السريرية للمرضى الخاضعين إلى خزعة نخاع العظم كانت شحوب بنسبة ٩١,٤% يتبعها الوهن الجسمي بنسبة ٥٩%. لقد كان التشخيص النسجي وحسب الترداد كالآتي: نخاع عظم عادي في ٢٨,٢% و ورم لمفي في ١١,١%. أبيضاضات حادة في ٩,٤% واضطرابات نخاعية تكاثرية في ٩,٤%. أبيضاضات مزمنة في ٥,١٢% ، ورم نقي متعدد في ٣,٤% و نقائل الأورام في ٢,٥٦% ومتلازمة خلل تنسج النخاع وفقر الدم الضخم الارومات ١,٧١% لكل منها ولا تنسج خلايا الحمر النقي (الخالص) وكذلك التهابات حبيبية ٠,٨٥% لكل منهما.

ولقد ترافقت الابيضاضات الحادة وعلى الأغلب في الحقب الأولى والثانية من العمر وتواجدت الأورام اللمفية و الابيضاضات المزمنة واضطرابات النخاع التكاثرية في الحقب الرابعة والخامسة وتواجدت متلازمة خلل تنسج النخاع في حقب الأعمار الأكبر إي الخامسة والسادسة. لقد شوهدت ورم نقي متعدد ونقائل الأورام في الحقب السادسة والسابعة. فيما تناثرت الاضطرابات الأخرى بصورة عشوائية.

الاستنتاج: إن خزع نخاع العظم هي وسيلة عدوانية مع احتمالية القليل من المضاعفات المعروفة ولكن لها قدرات تشخيصيه عالية وأهمية في علاجات ومتابعة مختلف الحالات الورمية واللامرضية. نسبة عالية من الحالات في هذه الدراسة أظهرت نخاع عظمي سليم هذا يظهر الدلالة المفرطة لعمل خزعة نخاع العظم. هذا يؤكد على أهمية التواصل ألسريري المرضي وتحليل المعطيات والبيانات لكل حالة.

Bone marrow trephine was first performed in 1903 by Piance who punctured the epiphysis of the femur by trocar. Arikin recommended the use of needle for bone marrow examination in 1929 and thereafter open biopsies were abandoned. This allows complete assessment of marrow architecture and the pattern of distribution of any abnormal infiltrate and for the detection of focal bone marrow lesions[1,2].

For bone marrow interpretation, pathologist should be provided with the history, clinical finding, peripheral blood picture and bone marrow aspirate examination[3]. The pathologist also should be familiar with the normal marrow histology to understand the pathological process[4].

A bone marrow trephine biopsy is an uncomfortable procedure for the patient and carries few adverse effects. The complications of bone marrow biopsy that may be encountered are excessive hemorrhage, infection and breaking of the needle within the bone[5,7]. Therefore it should be performed only when there is a clear clinical indication [5,6]. Such indications include inadequate or failed aspirate as in cases of dry aspirate, need for accurate assessment of marrow cellularity as to determine the extent of bone marrow damage in patients exposed to radiation, drugs, chemical or other myelotoxic agents, in suspected bone marrow fibrosis, in cases that need studying bone marrow architecture and determination of the pattern of infiltration[5], monitor the efficacy of treatment of certain conditions, assessment of the stage or progression of certain diseases and tumors including lymphomas and certain non-hematopoietic malignancies as neuroblastoma and other childhood tumors[7], to monitor the recovery process in patient undergoing bone marrow transplantation or marrow-ablative chemotherapy, and lastly it is also an important diagnostic procedure in cases of fever of unknown origin[8,9].

Trephine biopsy is usually carried out from the posterior superior iliac spine, with the patient in the left or right lateral position and the knee drawn up. The alternative site is just below the anterior superior iliac spine with the patient in supine position[5]. These sites carried out successfully in children and adult, while for neonate, a modified technique applicable to the tibia has been described[10].

There are different types of trephine bone marrow needle, example Jamshidi needles, Goldenberg SNARECOIL Bone marrow biopsy needle, ISAN and ACRI bone marrow biopsy

needles, Monoject bone marrow aspiration and biopsy needles, Lee Lok Bone Marrow Biopsy and Harvest Needle, Core-Lock Bone Marrow Biopsy Systems[11].

The biopsy should contain at least 5 to 6 intertrabecular spaces and should be at least 2-3 cm[1]. 1.5-2 cm is also acceptable length for adequate marrow biopsy[12-14].

The aim of the study is to evaluate the frequency, age distribution and document the histological pattern of various hematological disorders reported in bone marrow biopsy.

Material and methods

This is a retrospective and prospective study in which trephine bone marrow biopsies had been collected from Razkary hospital in Irbil from 2000 to 2007. The biopsies were performed for different clinical and laboratory indications. The relevant information and demographic data were collected from the laboratory request forms.

The retrospective cases were retrieved from laboratory archive. Blocks were re-cut, stained and reexamined. While the prospective cases started from 2004 in which the trephine biopsies had been carried out by the clinicians. The site of the biopsies was the posterior superior iliac crest. The average length of the biopsies were 0.5 to 2 cm. Biopsies were fixed in 10% formalin solution, kept for 24 hours then decalcified in 5% nitric acid for 3 to 4 hours, processed in automated tissue processor, then stained by routine hematoxylin and eosin stain.

The results were analyzed according to the number and percentage of different parameters.

Results

Bone marrow trephine biopsies of 117 cases were included in this study. There were 70 (59.83%) male and 47 (40.17%) females. The overall male to female ratio was 1.49:1. The mean age of patients who underwent trephine biopsy was 46.16 year with a range between 2 to 76 years. Majority of cases were in the 4th and 5th decades. The detailed distribution of age group and sex are shown in table (1).

Table (1): Age and sex distributions of the study sample.

Age	Male		Female		Total	
	No	%	No	%	No	%
0 – 10	3	(2.56)	0	(0.0)	3	(2.56)
11 – 20	4	(3.41)	7	(5.98)	11	(9.40)
21 – 30	8	(6.83)	8	(6.83)	16	(13.67)
31 – 40	10	(8.54)	5	(4.27)	15	(12.82)
41 – 50	12	(10.25)	8	(6.83)	20	(17.09)
51 – 60	13	(11.11)	11	(9.40)	24	(20.5)
61 – 70	13	(11.11)	6	(5.12)	19	(16.23)
71 – 80	7	(5.98)	2	(1.70)	9	(7.69)
Total	70	(59.83)	47	(40.17)	117	(100)

The commonest indication for bone marrow biopsy was pallor, which was seen in 107 (91.4%) of cases, followed by generalized body weakness, seen in 69 (59.0%) of cases, followed by other clinical and laboratory indications, as illustrated in table (2).

Table (2): Distribution of the study sample according to the main clinical and laboratory indications of bone marrow biopsy.

Clinical and lab indications	No of cases	% of cases
Pallor	107	(91.4)
Body weakness	69	(59.0)
Fever	51	(43.6)
Splenomegaly	35	(29.9)
Hepatomegaly	17	(14.5)
Lymphadenopathy	16	(13.6)
Bleeding	15	(12.8)
Increase ESR	15	(12.8)
Staging of malignancy	14	(11.9)
Pancytopenia	13	(11.1)
Blast in peripheral blood	12	(10.2)

The biopsies were examined by 2 pathologists independently with emphasis on the adequacy of the specimen, cellularity, proportion of hematopoietic cells, presence of atypical cells, abnormal proliferative process, presence of granuloma or microorganism, and abnormal infiltration of marrow biopsy.

The biopsies were adequate for establishment of diagnosis in 106 samples (90.6%), while in 11 samples (9.4%) the biopsies were inadequate, composed mainly of fibrocartilagenous tissue with no marrow elements. Few cases were due to processing or staining artifact.

The most frequent final diagnoses were malignancy of varying types (lymphoma, leukemias, chronic myeloproliferative disorders, multiple myeloma, metastasis and myelodysplastic syndrome) which was seen in 50 (42.7%), followed by normal bone marrow biopsy as it was seen in 34 (29.05%) of the biopsies. Others are illustrated in table (3).

Regarding the age distribution of different bone marrow diseases: in acute leukemia, majority of cases were seen in young age groups (1st and 2nd decades), whereas the chronic myeloproliferative disorders (including CML), chronic leukemias and lymphomas were identified in 4th and 5th decades of life. Myelodysplastic syndrome occurs in higher age groups, 5th and 6th decades, while the metastatic deposits and multiple myeloma were seen in 6th and 7th decades. Other disorders were distributed randomly in different age groups (table 4).

Table (3): Distribution of the number of cases according to the final diagnosis.

Diagnosis	No	%	Sub typing	No	%
Lymphomas	13	11.1	Lymphoplasmocytic Mixed small & large Small cell Non classified	4 4 2 3	3.42 3.42 1.71 2.56
Chronic myeloproliferative disorders	11	9.40	CML Myelofibrosis Essential Thrombocythaemia CMPD unclassifiable	6 3 1 1	5.12 2.56 0.85 0.85
Acute leukemia	11	9.40	AML ALL Unclassified	5 3 3	4.27 2.56 2.56
Chronic leukemia	6	5.12	CLL Hairy Cell Leukemia Prolymphocytic leukemia	3 2 1	2.56 1.71 0.85
Multiple myeloma	4	3.42			
Metastatic focus	3	2.56	Prostate Breast GIT	1 1 1	0.85 0.85 0.85
Myelodysplastic syndrome	2	1.71	Refractory anemia Refractory anemia with excess blasts	1 1	0.85 0.85
Normal bone marrow	34	29.05			
Insufficient for diagnosis	11	9.40			
Hyperplastic bone marrow	9	7.69			
Aplastic anemia / Hypoplastic bone marrow	9	7.69			
Megaloblastic anemia	2	1.71			
Pure red cell aplasia	1	0.85			
Granulomatous inflammation	1	0.85			
Total	117	100			

Table (4): Age group distribution according to the final diagnosis.

Diagnosis	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	Total	%
Lymphomas			2	2	2	5	2		13	(11.11)
Chronic myeloproliferative disorder				1	4	5	1	1	11	(9.40)
Acute leukemia	1	3	5				1	1	11	(9.40)
Chronic leukemia					2	1	3		6	(5.15)
Multiple myeloma							2	2	4	(3.42)
Metastatic							2	1	3	(2.56)
Myelodysplastic syndrome						1	1		2	(1.70)
Normal bone marrow	1	4	3	3	7	8	4	3	34	(29.05)
Insufficient for diagnosis			3	4	3		1		11	(9.40)
Hyperplastic bone marrow		2	1		2	2	1	1	9	(7.69)
Aplastic anemia / Hypoplastic bone marrow	1	2	2	3		1			9	(7.69)
Megaloblastic anemia				1			1		2	(1.70)
Pure red cell aplasia						1			1	(0.85)
Granulomatous inflammation				1					1	(0.85)
Total	3	9	16	15	20	24	19	9	117	(100)

Discussion

Bone marrow trephine biopsy is an indispensable tool for the diagnosis of various hematological diseases. To provide optimal results, the finding should be correlated with pertinent clinical and laboratory information. It can be performed in different age groups. In this study, various age groups were included; the mean age of this study was 46.16 year, reflecting the predominant age groups which are the 4th and 5th decades. This finding was higher than other studies [15-17], probably due to the relatively high number of hematological malignancies in this study. Regarding the gender, there was a male predominance with a ratio of 1.49:1 female. Slightly lower results were seen in other studies [15,16,18].

Pallor was the most common clinical feature of patients who underwent bone marrow trephine biopsy (seen in 91.4% of cases), solely or associated with other features. This agrees with other studies[15,16,19]. Generalized body weakness ranked the second frequent symptom and was present in 59.0% of cases. The latter was the main presenting symptom in another study[18]. The least common clinical feature was bleeding, which was the presenting symptom in 12.8% of cases. This is similar to another study[18].

Regarding the final diagnosis, the reporting of a normal bone marrow was reached in 29.05% of the biopsies. This is a relatively high percent in comparison with another study [18] and may reflect the overindication of marrow biopsy in our locality probably related to lack of proper clinicopathologic coordination.

Lymphoma was the second diagnostic report seen in 11.1%. This is similar to another study which shows the highest percent of lymphoma[16]. All were non-Hodgkin's lymphoma. The majority of these cases were lymphoplasmocytic lymphoma 4 (3.42%) cases and mixed small and large cell lymphoma 4 (3.42%) cases. They show a predominant diffuse and, to less extend, nodular pattern of infiltration. Similar results were reported by others [20-22]. In 3 (2.56%) cases the specific type of lymphoma could not be achieved and further immunohistochemical stains were recommended.

Acute leukemias ranked third by 9.40% of biopsies. The majority of those patients were in 1st and 2nd decades and mostly acute myeloid leukemia 5 (4.27%). While cases of acute lymphoblastic leukemia were seen in only 3 (2.56%). However; in 3 cases definitive typing of acute leukemia cannot achieved by bone marrow trephine biopsy alone. Similar findings were reported by other studies

[18,19,23,24] and slightly higher finding by others [15].

The chronic myeloproliferative disorders (CMPDs) are another group commonly diagnosed on histopathological examination of trephine bone marrow biopsies. The 2001 WHO classification system of chronic myeloid neoplasms classified chronic myeloproliferative disorders into the four classical MPDs (chronic myelogenous leukemia (CML), polycythaemia vera, essential thrombocythemia and chronic idiopathic myelofibrosis) as well as chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES) and CMPD unclassifiable. The central and shared feature in CMPDs is effective clonal myeloproliferation (that is peripheral blood granulocytosis, thrombocytosis or erythrocytosis) which is devoid of dyserythropoiesis, granulocytic dysplasia or monocytosis[25].

As for CML cases the histological picture shows hypercellular marrow with granulocytic hyperplasia and loss of fat cells. Reticulin is increased and may be confused with primary myelofibrosis[17]. In our study CML was diagnosed in 6 (5.12%) patients. Regarding myelofibrosis in which bone marrow aspirate usually shows “dry tap” and so trephine biopsy is the ultimate diagnostic tool in this condition. In our series, 3 (2.56%) cases were diagnosed as myelofibrosis, comparable to that of other studies[18,26,27,28]. We encountered 2 (1.71%) cases that were labeled as unclassified myeloproliferative disorders.

Chronic leukemia, including 3 cases of chronic lymphocytic leukemia (2.56%), 2 cases of hairy cell leukemia (1.71%), and 1 case of prolymphocytic leukemia (0.85%). All represent 5.12% of the studied group. This is similar to another study[18].

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorders which generally occur in older adults but may affect children. Myelodysplastic syndrome is characterized by ineffective hematopoiesis, morphological cell dysplasia (dyserythropoiesis; dysgranulopoiesis; dysmegakaropoiesis), peripheral blood cytopenias, progressive bone marrow failure and a tendency to progress to acute myelogenous leukemia[29,30]. According to the French-American-British (FAB) classification which was published in 1976 and revised in 1982 and WHO classification in late 1990s, cases were classified into 5 categories. These are refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML)[31]. In our study we reported myelodysplastic syndromes in 2 (1.71%) of cases, one is refractory anemia and the other is refractory anemia with excess blasts. The bone marrow findings were either hyper or hypocellular with multilineage dysplasia. This was similar to others[15,26].

As for bone marrow aplasia/ hypoplasia, we reported 9 cases (7.69%) and was seen in different age groups suggesting the variety of underlying causes. This is similar to other studies[18,20], but is lower than 2 other studies[19,26]. Determination of whether the aplasia was primary or secondary cannot be achieved by bone marrow biopsy alone; it needs clinical coordination.

Pure red cell aplasia was seen in 0.85% of cases. This is similar to other studies[24,32].

Bone marrow hyperplasia was encountered in nine cases (7.69%), 3 of them showed erythroid hyperplasia alone (as a result of the hemolytic process) and the rest showed pan hyperplasia of all three elements (probably due to hypersplenism). Megaloblastic anemia was diagnosed in 1.70% of cases. These numbers are lower than in another study[18].

The diagnosis of multiple myeloma in marrow biopsy depends upon extent of plasma cell infiltration, pattern of infiltration and cytological features of plasma cells[1,33]. Trephine biopsy in this disorder is an essential investigation. However; in cases in whom an aspirate permits a definitive diagnosis, the trephine biopsy is important as a baseline for comparison with repeated biopsies during follow up[5]. In our study 3.42% of cases were diagnosed as multiple myeloma. This is similar to two other studies[15,18].

The bone marrow biopsy is considered a sensitive technique for detecting metastatic tumors. It is also performed for staging purposes at the time of diagnosis in a number of solid tumors such as neuroblastoma in children and tumors of breast, stomach, colon, kidney, prostate, lung and lymphoma in adults [2,34]. The problems and pitfalls in the interpretation of metastatic deposits on bone marrow biopsy could arise because of some normal components of bone marrow like megakaryocytes, crushed erythroid cells, osteoblasts, osteoclasts, macrophages and fibroblasts may resemble with the tumor deposits [1]. In our study 3 (2.56%) known cases of solid body tumor were found to have metastatic deposits of adenocarcinma (prostate, breast and gastrointestinal tract). This finding coincides with other studies[15,17,35].

Granulomatous lesion was the least common pathological diagnosis which was present in 0.85% of cases. This histological finding is seen in a variety of conditions including tuberculosis, sarcoidosis, Hodgkin's disease, cat scratch disease, Q fever, brucellosis, leprosy, syphilis and typhoid fever[5,36-39]. There are no characteristic morphological features which allow reliable etiologic diagnosis of bone marrow granulomas[40,41]. This is similar to two other studies which show infrequent granuloma finding in bone marrow trephine biopsy[40,41,42], but unlike two other studies which show preponderance of granulomatous inflammation[17,18].

Inadequate biopsies were seen in 9.40% of cases. These were due mainly to absence of bone marrow element, or due to processing and staining artifact which obscured the histological picture. This is comparable to another [18].

Conclusion

Bone marrow trephine biopsy is an invasive procedure with few known complications, but is a valuable diagnostic tool in the diagnosis, staging, management and follow up of various types of conditions both neoplastic and non-neoplastic. High percentage of cases in our study show normal marrow finding, this may reflect overindication of marrow biopsy, such finding urge for more clinicopathological coordination and data analysis.

References

1. Bain BJ, Clark DM, Lampert IA, et al. Bone marrow pathology 3rd (ed), Blackwell Science Ltd. 2001: 5-7.
2. Nanda A, Basu S, and Marwaha N. Bone marrow trephine biopsy as an adjunct to bone marrow aspiration. J Assoc Physicians India 2002; 50: 893-5.
3. Cotelingam JD. Bone marrow biopsy: interpretive guidelines for the surgical pathologist. Adv Anat Pathol 2003; 10: 8-26.
4. Brown DC, and Gatter KC. The bone marrow trephine biopsy: a review of normal histology. Histopath 1993; 22: 411-422.
5. Bain BJ. Bone marrow trephine biopsy. J Clin Pathol 2001; 54: 737-742.
6. Malempati S, Joshi S, Lai S, et al. Bone Marrow Aspiration and Biopsy. N Engl J Med 2009; 361:e28.
7. Http://www.myoclinic.com. Accessed on 2-4-2009.
8. Manan MU, Khaliq MA, Ahmed S, et al. Diagnostic significance of bone marrow examination: A nine year experience. Ayub Med Coll 2000; 12; 43-45.
9. Sharma B K, Kumori S, Varma S C, et al. Prolonged undiagnosed fever in Northern India. Trop Geogr Med 1992; 44: 32–36.
10. Sola CM, Rimsza LM, and Christensen RD. A bone marrow biopsy technique suitable for use in neonates. Br J Hematol 1999; 107: 458-460.
11. http://www.pathology.vcu.edu/. Accessed on 12-1-2010.
12. Brynes RK, Mckenna RW, and Sundbeerg RD. Bone marrow aspiration and trephine biopsy: an approach to a through study. Am J Clin Pathol 1978; 70: 753-759.
13. Islam A. Manual of bone marrow examination-Amsterdam overseas publishers association, 1997.
14. Cambell JK, Matthews JP, and Seymour JE. Optimum trephine length in assessment of bone marrow involvement in patients with diffuse large cell lymphoma. Ann Oncol 2003; 14: 273-276.

15. Ali N, Khan MA, Anwar M. et al. Clinical assistance of Bone Marrow Examination in a secondary-care hospital. Pak Armed Forces Med J. 2004; 54(1): 51-53.
16. Syed NN, Moiz B, Adil SN, et al. Diagnostic importance of bone marrow examination in non-hematological disorders. J Pak Med Assoc Mar 2007; 57(3): 123-125.
17. Khan SA, Ahmed M, Afzal S, et al. Fever of unknown origin (FUO)-role of bone marrow trephine biopsy examination. Pak J Pathol Sep 2004; 15(3): 100-104.
18. Afzal S, ahmed M, Mubarik A, et al. Significance of bone marrow trephine biopsy in the diagnosis of hematological and non-hematological disorders. Pak J Pathol 2006;17(1):10-15.
19. Memon S, Shaikh S, and Nizamani MA. Etiological spectrum of pancytopenia based on bone marrow examination in children. J Coll Physicians Surg Pak. 2008; 18(3): 163-167.
20. Haddin WJ. Malignant lymphoma in Jordan: a retrospective analysis of 347 cases according to the World Health Organization classification. Ann Saudi Med 2005 Sep-Oct; 25(5): 398-403.
21. Durosinmi MA, Mabayoje VO, and Akinola NO. A review of histology of bone marrow trephine in malignant lymphomas. Niger J Med. 2003 Oct-Dec; 12(4): 198-201.
22. Hassan K, Ikram N, Bukhari KP, et al. The pattern of bone marrow infiltration in non-Hodgkin's lymphomas. J Pak Med Assoc. 1995 Jul; 45(7): 173-176.
23. Islam A, Catovsky D, Goldman JM, et al. Bone barrow biopsy changes in acute leukemia: Observations before chemotherapy. Histopath 1985; 9: 939-957.
24. Ikram N, Hassan K, and Bukhari KP. Spectrum of hematological lesions amongst children, as observed in 963 consecutive bone marrow biopsies. J Pak inst Med Sc. Dec 2002; 13(2): 686-690.
25. Tefferi A and Vardiman J W. Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia (2008) 22, 14–22.
26. Igbal W, Hassan K, Ikram N, et al. Etiological breakup in 208 cases of pancytopenia. J Rawal Med Coll Jun 2001; 5(1): 7-10.
27. Thiele J, Kvasnicka HM, Zankovich R, et al. Clinical and morphological criteria for the diagnosis of pre- fibrotic idiopathic (Primary) myelofibrosis. Ann Haematol 2001; 80: 160-165.
28. Kazi BM, Kazi F, and Anwar M. Bone marrow fibrosis (BMF): A new proposal for grading system. International J Pathol 2003; 1: 25-30.
29. Schmitt-Graeff A, Mattern D, Kohler H, et al. Myelodysplastic syndrome (MDS). Aspects of hematopathologic diagnosis. Pathology 2000 Jan; 21(1): 1-15.
30. Mufti GJ, Bennett JM, Bain BJ et al. Diagnosis and classification of myelodysplastic syndrome: International Working Group on Morphology of myelodysplastic syndrome (IWGM-MDS) consensus proposals for the definition and enumeration of myeloblasts and ring sideroblasts. Haematologica. 2008 Nov; 93(11):1712-7.
31. http://en.wikipedia.org/wiki/myelodysplasticsyndrome. Acessed on 20-2-2010.
32. Shuaib A, Omar M, Naeemullah S, et al. Pure red cell aplasia-a single center experience. Pak J Pathol 2005; 16(1); 10-13.
33. Bartl R, and Frisch B. Diagnostic morphology in multiple myeloma. Curr Diag Pathol 1995; 2: 222-235.
34. Burkhardt R, Frisch B, and Kettner G. The clinical study of micro-metastatic cancer by bone biopsy. Bull Cancer 1980; 67: 291-305.
35. Ozkalemkas F, Ali R, Ozkocaman V, et al. The bone marrow aspirate and biopsy in the diagnosis of unsuspected non-hematologic malignancy: A clinical study of 19 cases. BMC Cancer 2005; 5: 144.
36. Vilalta- Castel E, Valdes- Sanchez MD, Guerra-Vales JM, et al. Significance of granulomas in bone marrow: a study of 40 cases. Eur J Haematol 1988; 41: 12-14.

37. Bhargava V, and Farhi DC. Bone marrow granulomas: Clinicopathologic findings in 72 cases and review of the literature. Haematol Pathol 1988; 2: 43-50.
38. Mert A, Tabak F, Ozaras R. et al. Typhoid fever as a rare cause of hepatic, splenic, and bone marrow granulomas. Inter Med. 2004 May; 43(5): 436-439.
39. Miller AC, Chacko T, Rashid RM, et al. Fever of unknown origin and isolated noncaseating granuloma of the marrow: could this be sarcoidosis. Allergy Asthma Proc. 2007 Mar-Apr: 28(2): 230-235.
40. Bodem CR, Hamory BH, Taylor HM et al. Granulomatous bone marrow disease. A review of literature and clinicopathologic analysis of 58 cases. Medicine (Baltimore). 1983 Nov; 62(6): 372-383.
41. Vijnovich Baron IA, Barazzutti L, Tartas N, et al. Bone marrow granulomas. Sangre (Barc). 1994 Feb; 39(1): 35-38.
42. Basu D, Saravana R, Purushotham B, et al. Granulomas in bone marrow- a study of fourteen cases. Indian J Pathol Microbiol. 2005 Jan; 48(1): 13-16.

