불명열 환자에서 골수생검의 효용성 예측에 있어서 연령 요인

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Lower Diagnostic Value of Bone Marrow Biopsy in Children with Fever of an Unknown Origin

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Background: Diagnostic value of Bone marrow (BM) biopsies for fever of unknown origin (FUO) remain controversial and BM biopsies are difficult to perform in young patients. Our study aimed to elucidate the diagnostic yield of BM biopsies in FUO patients of all age, particularly for diagnosing hematological malignant diseases.

Methods: The medical records of 150 patients, hospitalized between January 1, 2008 and June 30, 2013, who underwent BM biopsies were evaluated to determine the cause of FUO. FUO was defined as fever (38.3°C, 101°F) either on several occasions during the 3 hospital days without a clear cause, after 1 week of invasive investigation, or after 3 outpatient visits. BM-specific diagnoses included those determined by BM biopsies (i.e., leukemia, lymphoma, myeloproliferative disease, myelodysplastic syndrome, aplastic anemia, and hemophagocytic lymphohistiocytosis).

Results: The final diagnoses of 24 patients (16%) were determined by BM biopsies; the majority included hematologic diseases and malignant neoplasms. Low hemoglobin levels, thrombocytopenia, bicytopenia, increased Lactate dehydrogenase (LDH) and ferritin levels, and ultrasonographic/computed tomographic abnormalities were significant risk factors ($P<0.05$). The young patient group (<18 years old) was safer from the tendency of BM biopsy diagnosis compared to adult patient group (>40 years old).

Conclusion: Some laboratory abnormalities were related to the BM biopsy diagnostic yield. Furthermore, pediatric age was an important factor for deciding to do not perform excessive BM biopsies in FUO cases.

Key Words: Fever of unknown origin, Bone marrow biopsy, Hematological malignancy, Age, Predictive factors

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Introduction

Despite advances in diagnostic techniques and research, determining the causes of fever of unknown origin (FUO) remains an unassailable challenge. In 1961, Petersdorf and Beeson established the definition of FUO [1]: an illness with a duration >3 weeks, fever >38.38°C (101.8°F) on at least 2 occasions, and an uncertain diagnosis after 1 week of hospitalization. However, a modified definition of the FUO

criteria was suggested in 1991, which reflected the current trend of conducting aggressive investigations during the early stages of febrile status and advancements in diagnostic tools [2]. Many non-invasive and invasive procedures, including laboratory tests, imaging studies, and biopsies were performed to determine the causes of FUO [3-6].

Traditionally, bone marrow (BM) biopsy has been one of the procedures to determine the cause of FUO. Moreover, hematologic malignancies and occult cancers or infections cannot be diagnosed without BM biopsies. BM biopsies have been considered as a secondary plan among various diagnostic methods due to its invasive character [7]. Previous studies have been conducted regarding the accuracy of the diagnostic yield of BM biopsies, which is considered as a relatively invasive procedure for FUO work-up. However, most of these previous studies were restricted to patients with FUO and human immunodeficiency virus (HIV) or mycobacterial infection, not immunocompetent patients [8,9].

In a recent study, anemia and thrombocytopenia were identified as predictable factors for effective BM biopsy in immunocompetent patients with FUO; the diagnostic yield was observed to be 23.7%, which was quite high in the modern FUO workup era [10]. Moreover, in a more recent study, the positive predictive factor of BM biopsies as useful diagnostic tools for FUO was determined using not only clinical manifestations and laboratory data, but imaging studies (i.e., computed tomography) as well [11].

Despite continuous efforts to confirm the diagnostic yield of BM biopsy during investigations of FUO, no studies have been currently published regarding age factors affecting the diagnostic yield of BM biopsies in FUO. The diagnostic yield of BM biopsies in children is important for deciding whether BM biopsies should be performed; the procedure itself is too invasive for children and hard to perform because of the need for anesthesia under poor general conditions (i.e., fever or sepsis). Therefore, we identified clinical and laboratory factors, especially age, to determine the predictive efficacy for increasing positive findings in BM biopsies and the cause of FUO.

Materials and Methods

The medical records of 150 patients, hospitalized in the Yonsei University Health System as the tertiary university hospital, between January 1, 2008, and June 30, 2013, who underwent BM biopsies were reviewed to determine the cause of FUO.

The newer definition of FUO was used in this study: (1) 3 outpatient visits, (2) 3 days of hospitalization without a clear cause, or (3) 1 week of "intelligent and invasive" ambulatory investigations [2]. Patients with a known HIV infection, history of hematological malignant disease, or those undergoing immunosuppressive therapy or organ transplantation were excluded.

The 150 patients were categorized into either the 'BM specific diagnostic group' or 'non-diagnostic group' by evaluating the BM biopsy pathology of each patient. A BM specific diagnosis was defined when all specific diagnoses were confirmed by the BM biopsy examination (i.e., leukemia, lymphoma, myeloproliferative disease, myelodysplastic syndrome, aplastic anemia, hemophagocytic lymphohistiocytosis, and BM involvement of solid tumors).

1) Diagnostic workup

A standardized diagnostic workup was conducted to confirm that the FUO included medical history reviews, clinical physical examinations, blood tests, urinalysis with urine cultures, chest radiography, abdominal ultrasonography, contrast-enhanced chest computed tomography (CT), abdominal-pelvic CT, positron emission tomography (PET)-CT, and echocardiogram. The routine blood test included a complete blood cell count with a differential leukocyte count, routine blood chemistry analysis (including lactate dehydrogenase and ferritin), erythrocyte sedimentation rate, C-reactive protein, blood cultures, and serology tests for cytomegalovirus and Epstein-Barr virus.

In our study, patients with anemia were determined using hemoglobin levels according to the following age-specific criteria: hemoglobin <10 g/dL in patients <6 years, <11 g/dL in patients aged 6-15 years, and <12 g/dL in patients >15 years. Patients who had both leukocytopenia

(i.e., white blood cell count <4,000/μL) and thrombocytopenia (i.e., platelet count $<10\times10^3$/μL) were defined as having a 'bicytopenia' state.

All imaging studies were categorized either as normal or abnormal. In the echocardiogram pericardial effusion, pericarditis and vegetation were considered abnormal. Abnormal results of the chest and abdominal image (i.e., chest X-ray, US, CT, PET-CT, echocardiogram) included hepatomegaly, splenomegaly, significant lymphadenopathy (appearing as non-reactive), definite infectious focus, and suspicious malignancies. However, only suspicious malignancies in the PET-CT image were categorized as abnormal.

2) Statistical analysis

Continuous variables were statistically represented as means with standard deviations. Univariate analyses, conducted to evaluate the differences between the groups based on baseline clinical variables, were performed with the Student t-tests for continuous variables and Chi-square test for categorical variables. We also calculated the odds ratios (OR) along with their *P*-values and 95% confidence intervals (CI) in the univariate analyses. In the multivariate analysis, a binary logistic regression test was applied to select variables, which were considered as independent and predictable factors for effective BM biopsy. All statistical evaluations in this study were conducted using SPSS statistical software version 18.0.0 (SPSS Inc., Chicago, IL, USA). All results with a *P*-value <0.05 were regarded to be statistically significant.

Table 1. Baseline variables of the study patients (n=150)

Characteristic	Value (Mean±SD, %)
Age (Mean±SD, yr)	38.4±26.6
Sex	
Male	86 (57.3)
Female	64 (42.7)
Symptoms	
URI (cough, sputum, rhinorrhea)	59 (39.3)
Bone pain	44 (29.3)
Rash	34 (22.7)
GI (nausea, vomiting, diarrhea)	22 (14.7)
Weight loss	7 (4.7)
Sweating	5 (3.3)
Signs	
Splenomagaly	32 (21.3)
Lymphadenopathy	20 (13.3)
Hepatomegaly	13 (8.7)

UR, upper respiratory infection; GI, gastrointestinal.

Results

1) Demographics

The baseline characteristics and variables of the 150 patients (86 men and 64 women), with an age from 1 year old to 89 years old, are summarized in Table 1. The most common symptom and sign of our population were upper respiratory infection symptoms and splenomegaly, respectively.

2) Diagnoses after bone marrow biopsy for patients with fever of unknown origin

Hematological malignant disorders were observed to be the most dominant diagnosis, which included non-Hodgkin's lymphoma (n=11) and hemophagocytic lymphohistiocytosis (n=6; Table 2). The final diagnoses were established after BM biopsies in 24 patients (16.0%).

3) Risk factors to determine the diagnostic yield of bone marrow biopsy

The clinical and biological characteristics, considered as predictable factors for deciding whether or not to perform

Table 2. Final diagnoses determined by bone marrow examination

Final diagnosis	Patinets, No. (n=24)
Leukemia	1 (4.2)
Acute lymphoblastic leukemia	0
Acute myeloid leukemia	1
Non-Hodgkin lymphoma	11 (45.8)
Peripheral T-cell lymphoma	1
Diffuse large B cell lymphoma	6
NK/T cell lymphoma	1
Burkitt lymphoma	1
Intravascular lymphomatosis B cell	1
Follicular lymphoma	1
Myeloproliferative disorder	2 (8.3)
Chronic myeloid leukemia	2
Myelodysplastic syndrome	2 (8.3)
Solid malignant neoplasms	1 (4.2)
Neuroblastoma	1
Aplastic anemia	1 (4.2)
Hemophagocytic lymphohistiocytosis	6 (25)
Total	24 (100%)

BM biopsy, are listed in Table 3. Initial hemoglobin and platelet levels were significantly lower in the BM diagnostic group than the non-diagnostic group in adult group. Lactate dehydrogenase levels were higher in the BM diagnostic group compared to the non-diagnostic group in child group. The symptoms (i.e., rash and bone pain) and signs (i.e., lymphadenopathy, hepatomegaly, and splenomegaly) of the patients were not significantly different, excluding bone pain in child group. Most imaging studies were more likely to be abnormal in adult BM diagnostic group.

Anemia, thrombocytopenia (platelet $<10\times10^3/\mu L$), bicytopenia (leukocytes $<4,000/\mu L$ and platelet $<10\times10^3/\mu L$),

Table 3. Clinical and biological characteristics of patients with bone marrow biopsy contribution

Characteristic	Adult group[a]			Child group[a]		
	BM diagnostic (n=21, %)	BM non-diagnostic (n=76, %)	*P*-value[b]	BM diagnostic (n=3, %)	BM non-diagnostic (n=50, %)	*P*-value[b]
Age (Mean±SD, yr)	58.7±14.0	54.0±18.0	0.27	4.2±1.9	8.2±4.6	0.15
URI	6 (28.6%)	28 (36.8%)	0.48	1 (33.3%)	24 (48.0%)	0.62
Bone pain	7 (33.3%)	28 (36.8%)	0.77	2 (66.7%)	7 (14.0%)	<0.05[b]
Lymphadenopathy	2 (9.5%)	12 (15.8%)	0.47	0	6 (16.0%)	0.52
Hepatomegaly	3 (14.3%)	6 (7.9%)	0.37	1 (33.3%)	3 (6.0%)	0.08
Splenomegaly	5 (23.8%)	19 (25.0%)	0.91	1 (33.3%)	7 (14.0%)	0.36
Abnormal echocardiography	6 (28.6%)	2 (2.6%)	<0.05[b]	0	0	-
Chest or Abdomen image abnormality	19 (90.5%)	57 (75.0%)	0.31	2 (66.6%)	11 (22.0%)	0.15
Suspected malignancy in PET-CT	8 (38.1%)	5 (6.6%)	<0.05[b]	1 (33.3%)	0	0.08
Leukocyte count (/μL)	9,952.9±11,687.1	10,467.5±7,098.0	0.80	4,463.3±4,409.4	8,138.4±8,418.4	0.46
Lymphocyte count (/μL)	1,433.7±1,115.9	1,577.4±1,991.1	0.77	2,256.7±1,898.7	2,009.2±1,313.8	0.76
Hb (g/dL)	10.4±2.1	12.0±2.2	<0.05[b]	10.3±1.5	11.7±1.5	0.14
Platelet ($\times10^3/\mu L$)	148.8±119.5	265.5±184.5	<0.05[b]	150.3±107.3	347.5±180.7	0.07
CRP (mg/L)	107.9±88.5	73.0±92.0	0.12	11.0±14.0	25.2±33.3	0.47
LDH (IU/L)	385.8±213.7	306.8±178.0	0.09	592.7±148.5	338.4±183.0	<0.05[b]
Ferritin (ng/mL)	1,674.1±1,879.3	1,473.5±2,001.0	0.69	1,759.3±1,440.2	875.5±2,106.6	0.49

BM, Bone marrow; Hb, Hemoglobin; CRP, C-reactive protein; LDH, Lactate dehydrogenase.
[a]Adult group, >18 years old; Child group, ≤18 years old. [b]Statistically significant for BM diagnostic ($P<0.05$).

Table 4. Clinical and laboratory predictive parameters with bone marrow biopsy contribution

Clinical & biological characteristic	Adult group[a]		Child group[a]	
	Odds ratio (95% Cl)	*P*-value[b]	Odds ratio (95% Cl)	*P*-value[b]
Sex	1.54 (0.57-4.15)	0.46	1.10 (0.99-1.22)	0.55
Anemia[c]	5.49 (1.81-16.6)	<0.05[b]	3.07 (0.25-38.6)	0.39
Leukocytopenia[d]	2.03 (0.70-5.92)	0.24	4.25 (0.36-50.4)	0.26
Thrombocypotenia[d]	2.81 (1.01-7.84)	0.05	7.83 (0.54-113.0)	0.08
Bicytopenia[d]	3.40 (1.03-11.26)	0.07	12.0 (0.74-194.6)	0.16
C-reactive protein >100 (mg/L)	2.54 (0.95-7.80)	0.07	0.94 (0.88-1.00)	0.66
Lactate dehydrogenase >350 (IU/L)	3.53 (1.29-9.70)	<0.05[b]	1.18 (0.98-1.11)	<0.05[b]
Ferritin >500 (ng/mL)	8.08 (1.75-37.32)	<0.05[b]	8.40 (0.63-112.1)	0.14
Abnormal echocardiography	12.75 (2.16-75.30)	<0.05[b]	-	-
Chest or abdomen image abnormality	3.17 (0.67-14.87)	0.23	7.09 (0.59-85.69)	0.15
Suspected malignancy in PET-CT	12.53 (3.08-51.02)	<0.05[b]	-	-

[a]Adult group, >18 years old; Child group, ≤18 years old. [b]Statistically significant for BM diagnostic ($P<0.05$). [c]Anemia: under 6 years old; <10 (g/dL), 6 years to 15 years old; <11 (g/dL), over 16 years old; <12 (g/dL). [d]Leukocytopenia, Leukocytes $<4,000(/\mu L)$; Thrombocypotenia, Plt $<10\times10^3$ $(/\mu L)$; Bicytopenia, Leukocytes $<4,000(/\mu L)$ and Plt $<10\times10^3$ $(/\mu L)$.

increased LDH levels (>350 IU/L), increased ferritin levels (>500 ng/mL), and imaging abnormalities were also significant factors for predicting effective BM biopsy in adult group (all $P<0.05$; Table 4). However, only increased LDH levels (>350 IU/L) was significant factors for predicting effective BM biopsy in child group.

4) Multivariate analysis for risk factors

For the multivariate analysis with logistic regression analysis, we selected 6 variables that were considered as predictive factors (i.e., sex, age, anemia, bicytopenia, LDH, and image abnormality). The young adult group (18-40 years old; young adult [AYA] age group) was the lowest probability for a positive BM diagnostic yield for FUO. The children and adolescent group under 18 years old had an increased tendency of positive BM biopsy finding (hazard ratio [HR], 3.11; 95% confidence interval [CI], 0.25-39.59) compared to the AYA group; however, this relationship was not significant. And we also observed that under 18 years old group was safer from the tendency of BM biopsy diagnosis compared to over 40 years old group (HR, 8.227; 95% CI, 0.90-75.36). Low hemoglobin levels (HR, 8.66; 95% CI, 2.32-32.40), bicytopenia (HR, 5.21; 95% CI, 1.34-20.26), and increased LDH levels (HR, 10.71; 95% CI, 2.78-41.29) were determined to be independent predictive factors for diagnostic BM biopsy ($P<0.05$; Table 5).

Table 5. Multivariate analysis of patients with useful bone marrow biopsy result

Variables		BM - specific diagnosis	
		Hazard ratio	*P*-value[a]
Sex	Female	1	
	Male	1.399	0.585
Anemia	Normal	1	
	Abnormal	8.659	<0.05[a]
Bicytopenia	Normal	1	
	Abnormal	5.21	<0.05[a]
LDH	≤350 IU/L	1	
	>350 IU/L	10.71	<0.05[a]
Age	18-40 years old	1	
	<18 years old	3.11	0.381
	≥40 years old	8.227	0.062
Image abnormality[b]	Normal	1	
	Abnormal	2.912	0.17

LDH, Lactate dehydrogenase.
[a]Statistically significant for BM diagnostic ($P<0.05$). [b]Image abnormality; Chest or Abdomen image abnormality (ultrasonography or CT).

Discussion

In this study, we tried to confirm the diagnostic yield of BM biopsy in patients with FUO in all age groups. Until now, numerous studies that have been published regarding effective BM biopsies in patients with FUO were generally limited to adult patients [7,10-13]. However, BM biopsies are relatively difficult to conduct in young patients because of sedation, airway problems, and poor general conditions associated with systemic inflammatory response syndrome during FUO. However, BM biopsies should be performed despite procedural difficulties, if proven effective in younger patients with FUO, due to the higher incidences of hematological malignant diseases (i.e., acute lymphoblastic leukemia or lymphoma) in the BM of pediatrics patients compared to adult [14-16].

During the past decades, almost all large FUO studies regarding BM biopsy yields were conducted in adult patients [7,10-13]. In the 2 most recent reports, which were aimed at determining predictive factors of diagnostic BM biopsies, the study population included only adult patients [10,11]. Numerous studies involving pediatric participants have been published; however, the results of these studies were limited in the etiology or prognosis of FUO retrospectively [17,18]. Only a few studies have been published regarding the diagnostic yield of basic procedures in young patients with FUO. Especially, the report that focusing the diagnostic role of BM Biopsies in FUO was unprecedented. And in most reports, descriptions about the role of BM biopsies were limited to secondary option of FUO workup [19]. Hasan et al. was the only mentioned that several invasive procedures, including BM biopsies, were effective in 29% of pediatric patients with FUO [20]. Until now, no reports have been conducted to elucidate the diagnostic yield of BM biopsies in pediatric patients with FUO patients and the difference in the diagnostic yield of BM biopsies according to age (i.e., childhood vs. adulthood). Deciding whether or not to perform BM biopsies is dependent upon age fac-

tors, because of the higher incidence of hematologic malignancies and the difficulty and safety issues in pediatric age related to performing BM biopsies under anesthesia.

In this study, we determined the yield or efficacy of BM biopsies for diagnosing FUO in 3 age groups (i.e., children <18 years, 18-40 years or AYA group, and old age group >40 years old). We found that in spite of high incidence of hematological malignant diseases which can be confirmed by BM biopsies in younger patients, the pediatric group (<18 years old) had the lower probability for a positive BM diagnostic yield for FUO comparing the old age group (>40 years old). Therefore, the requirements for BM biopsies should be re-modified by considering the efficacy and safety aspects of the pediatric group (<18 years old).

We observed that anemia, bicytopenia, and increased LDH levels were independent predictive parameters for diagnostic BM biopsy in multivariate analysis. Hot et al. revealed that lower hemoglobin levels and platelet counts were associated with a higher possibility of diagnostic BM biopsies [10]. The authors of this study performed the basic FUO workup, including medical history reviews, clinical physical examinations, laboratory results, but not imaging investigations. Recently, CT was regarded as an initial investigation tool for evaluating FUO because of its relatively high diagnostic profit [3,13]. Furthermore, Ben-Baruch et al. reviewed the diagnostic yields of BM biopsies in extensive FUO workup processes using CT images [11]. In their multivariate analysis, lower hemoglobin and increased LDH levels were confirmed as positive indicators of diagnostic BM biopsies. Our results from the multivariate analysis were similar to those of recently published reports; lower hemoglobin levels, bicytopenia, and increased LDH levels were independent predictive factors for effective BM biopsies. The final diagnoses in this study, which were confirmed by BM biopsies, were mostly hematologic disorders. Laboratory factors (i.e., lower hemoglobin levels, bicytopenia, or increased LDH levels) all suggested bone marrow involvements of hematologic disorders, which was consistent with previous studies.

For investigations of FUO, X-ray and ultrasonography are regarded as first line imaging workup followed by CT and magnetic resonance imaging (MRI). These primary anatomic imaging studies play critical roles in diagnosing or guiding the biopsy in patients with FUO; however, the sensitivity of these initial imaging tools is inferior [7]. Recently, the contribution of PET/CT for FUO evaluations has increased because of its usefulness in the field of oncology and its ability to determine nonspecific inflammation and malignancy. Kouijzer et al. observed a high sensitivity (89-100%) and usefulness of PET/CT imaging for FUO investigations in a review of 10 past studies related to PET/CT in FUO [21]. In one of the pediatric studies, PET or PET/CT was determined to be clinically useful (45%) as a diagnostic tool for evaluating pediatric FUO and unexplained inflammation [22]. However, PET/CT was not proved to be an independent factor for predicting positive BM biopsy findings in this study, which implies that the probability of hematologic malignancies was high. These findings were not consistent with previously reports, probably due to several factors and biases. Firstly, X-ray, ultrasonography, CT, and PET/CT images were used simultaneously during the FUO workup and were not conducted sequentially. Therefore, the efficacy of PET/CT might be biased. Secondly, diagnoses would be direct and additional invasive procedures (i.e., BM biopsies) can be avoided if signs of malignancy or FUO are observed in the PET/CT images.

A limitation of this study was that it was a retrospective study, which was conducted at a single center. However, strengths of this study were that the diagnostic procedures were conducted in a homogeneous physicians group at a tertiary center and focused on the BM biopsy yield in the modern era using various effective laboratories and imaging workups. Moreover, we focused on age factors to determine the BM biopsy diagnostic yield, which had not been studied previously according to the best of our knowledge.

In conclusion, certain laboratory abnormalities that determined the diagnostic yield of BM biopsies were confirmed in this study. In addition to such abnormalities, the BM biopsy can be less likely to yield occult malignancies in pediatric group (<18 years old) comparing the older age group (>40 years old).

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