

Yield of Bone Marrow Examination in Diagnosing the Source of Fever of Unknown Origin

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Background: Fever of unknown origin (FUO) still remains a diagnostic challenge, while diagnosis may remain obscure for several weeks or months. The role of tissue biopsy is crucial in the diagnostic approach. We report a series of 130 consecutive patients with FUO who had undergone a bone marrow biopsy (BMB).

Methods: Among 280 consecutive nonimmunocompromised patients hospitalized between 1995 and 2005 for a febrile illness of uncertain cause, lasting at least 3 weeks, with no diagnosis after an appropriate minimal diagnostic workup, 130 underwent BMB.

Results: Overall, a specific diagnosis was achieved by BMB and histological examination in 31 cases (diagnostic yield, 23.7%). Three types of diseases were found: hematological malignant diseases in 25 cases, including 19

patients with malignant lymphoma, 4 with acute leukemia, 1 with hairy cell leukemia, and 1 with multiple myeloma; infectious diseases in 3 cases; systemic mastocytosis in 2 cases; and disseminated granulomatosis in 1 case. Thrombocytopenia (odds ratio, 4.9; 95% confidence interval, 1.04-9.30) and anemia (odds ratio, 3.24; 95% CI, 1.13-9.34) were the most reliable predictive factors regarding the usefulness of BMB. Bone marrow cultures had very limited value in our cohort. Finally, corticosteroid use did not seem to affect the yield of BMB.

Conclusions: Bone marrow biopsy is a useful technique for the diagnosis of prolonged fever in immunocompetent patients. Thrombocytopenia and anemia seem to be correlated with the value of this test.

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IN 1961, PETERSDORF AND BEESON¹ published their classic article on fever of unknown origin (FUO) and established criteria that have effectively delineated this entity: an illness of at least 3 weeks' duration, with fever (temperature >38.3°C on several occasions), and no established diagnosis after 1 week of hospital investigation. The diagnostic workup often involves many noninvasive and invasive procedures that sometimes fail to explain the fever. Indeed, there are more than 200 causes of FUO, many of which can involve the bone marrow.² A panel of laboratory tests including cultures and serologic examination, imaging studies, aspiration, or biopsies of cutaneous lesions and lymph nodes can provide clues to the diagnosis of fever. Nevertheless, fever still persists and remains unexplained in some patients.³ The yield of bone marrow examination in these patients remains unknown. Bone marrow biopsy (BMB) has been shown to be a safe and useful diagnostic procedure for FUO in patients with human immunodeficiency virus (HIV) infection.^{4,5} However, its usefulness in the diagnosis of FUO in immunocompetent patients has not been sufficiently assessed. Its diagnostic yield and indications remain controversial.⁶ Bone marrow biopsy could be a rapid test for clinical decision making in suspected cases of mycobacterial infection or hematological malignant diseases. Indeed, involvement of the marrow may be the first indication of the existence of lymphoma, an emerging cause of FUO. We describe herein the yield of bone marrow examination in a subgroup of 130 patients among 280 nonimmunocompromised patients presenting to a single tertiary care center with a prolonged, unexplained febrile illness. This study compares patient groups according to the yield of BMB in the diagnosis of FUO.

ciency virus (HIV) infection.^{4,5} However, its usefulness in the diagnosis of FUO in immunocompetent patients has not been sufficiently assessed. Its diagnostic yield and indications remain controversial.⁶ Bone marrow biopsy could be a rapid test for clinical decision making in suspected cases of mycobacterial infection or hematological malignant diseases. Indeed, involvement of the marrow may be the first indication of the existence of lymphoma, an emerging cause of FUO. We describe herein the yield of bone marrow examination in a subgroup of 130 patients among 280 nonimmunocompromised patients presenting to a single tertiary care center with a prolonged, unexplained febrile illness. This study compares patient groups according to the yield of BMB in the diagnosis of FUO.

METHODS

From January 1995 through December 2005, we collected the clinical records and the pathological charts of 280 consecutive patients who

showed FUO and were referred to 2 internal medicine units located in a tertiary care center in France. Then, we selected the patients who had undergone a BMB as part of the diagnostic procedure. To be included in the final database, patients had to meet 3 criteria: first, they had to meet the first 2 criteria of the FUO definition of Petersdorf⁷: (1) duration of illness of more than 3 weeks before diagnosis and (2) repeatedly documented body temperature exceeding 38.3°C. A standardized minimal diagnostic workup was required to retain the diagnosis of FUO. This minimal workup included history reviews, clinical examinations, routine laboratory tests, urinalysis, urine cultures, chest radiography, and abdominal ultrasonography. The routine laboratory tests included complete blood cell count including differential leukocyte and platelet count; routine blood chemistry analysis including lactate dehydrogenase; measurement of bilirubin and liver enzyme levels; assessment of erythrocyte sedimentation rate; antinuclear antibody detection; measurement of rheumatoid factor and angiotensin-converting enzyme levels; routine blood cultures ($\times 3$) while not receiving antibiotics; cytomegalovirus IgM antibody and heterophile antibody tests; tuberculin skin test, and HIV serologic analysis. Finally, the urine analysis included microscopic analysis and culture.

DEFINITIONS

Recurrent or episodic fever was defined as cyclical fever with apparent remission of the disease and fever-free intervals of at least 2 weeks.⁸ Patients with nosocomial fever, known HIV infection, or history of hematological malignant diseases or who were immunocompromised were excluded. Immunodeficiency encompassed the following conditions: neutropenia (white blood cell count $< 1000/\mu\text{L}$ and/or granulocyte count $< 500/\mu\text{L}$ [to convert to $\times 10^9/\text{L}$, multiply by 0.001]), hypogammaglobulinemia (IgG $< 50\%$), and solid organ transplant recipients.

Bone marrow biopsies were performed by puncture of the posterior iliac crest using a Jamshidi needle. Sections were sent in formalin solution for histologic processing. Sections of core biopsy and particle and preparation samples were stained with hematoxylin-eosin. Immunohistochemical assay was only performed if a malignant lymphoma was suspected. All archived slides were reviewed in a blinded manner by a single histologist (M.F.). Bone marrow aspirate was routinely stained with Giemsa.

MICROBIOLOGICAL STUDY

Bone marrow aspirates were directly inoculated in mycobacterial culture medium (BACTEC; Becton, Dickinson and Company, Franklin Lakes, New Jersey) for each patient at the bedside.

To confirm the diagnosis of the febrile illness, all patients were seen at 6 months and 1 year after the hospital discharge. Many of them were followed up at the same center, and clinical and biological data were gathered for each patient visit.

STATISTICAL ANALYSIS

The primary end point was BMB contribution with 2 categories: useful or not useful. The χ^2 test and Fisher exact test were used to compare differences between both groups based on baseline clinical variables. In addition, continuous variables were presented as medians and interquartile ranges and were compared using 1-way analysis of variance (ANOVA) or the Kruskal-Wallis test and pairwise analyses with the Mann-Whitney test and ANOVA when appropriate. A logistic regression model was used to predict the probability of performing a useful BMB. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for independent variables in the model. The area under the re-

Table 1. Demographic Characteristics and Baseline Variables, and Final Diagnosis for 280 Patients With Fever of Unknown Origin

Characteristic	Value (N = 280)
Age, median (interquartile range), y	55.7 (20-88)
Sex, No. (%)	
Male	162 (57.8)
Female	118 (42.2)
Periodicity of fever, No. (%)	
Episodic	104 (37.1)
Continuous	176 (62.9)
No diagnosis, No. (%)	92 (32.8)
Final diagnosis, No. (%)	188 (67.2)
Infectious diseases	30 (15.9)
Neoplasia	57 (30.3)
Noninfectious inflammatory diseases	76 (40.2)
Miscellaneous	25 (13.6)

ceiver operating characteristic curve assessed the predictive accuracy of the model. Statistical analyses were performed using SPSS software version 12 (SPSS Inc, Chicago, Illinois). All statistical testing was performed using 2-tailed tests; $P < .05$ was considered statistically significant.

RESULTS

STUDY POPULATION

Over the last decade, 280 patients were hospitalized in our tertiary care center for the exploration of FUO. **Table 1** summarizes the demographic characteristics and diagnostic category for the 280 patients. Among the 280 patients, we identified 130 who had undergone a BMB during the workup of FUO. Then, we retrospectively reviewed the clinical and biological data of these 130 patients (77 men and 53 women), with age ranging from 20 to 88 years (mean age, 58.3 years). Forty-eight patients (37.6%) presented with a recurrent fever. Then, we reviewed 151 BMB results: some patients had undergone more than 1 biopsy (17 patients [13.1%] underwent more than 1 biopsy, 4 of whom underwent 3 biopsies). The mean duration of fever before the admission was 43 days (range, 21-350 days). Sixty-two patients (47.7%) were referred after extensive investigations in another hospital, and 68 (52.3%) were referred by their primary care physicians. The BMB was performed early (first days of the hospitalization, but with a fever duration of 57 days) in some cases because the patients were referred by another center and the physicians in charge of the patient suspected a malignant lymphoma.

Table 2 lists the final diagnosis and the diagnostic categories in all 130 patients. The diagnoses were subdivided according to the 5 classic categories. Overall, neoplasia (28.4%) and noninfectious inflammatory diseases (24.6%) constituted the most prevalent diagnostic categories.

BONE MARROW BIOPSY

A total of 151 bone marrow biopsies were performed. However, we limited our analysis to the first biopsy (130

Table 2. Final Diagnosis in a Cohort of 130 Patients With Fever of Unknown Origin

Final Diagnosis	Patients, No. (%)
Infectious diseases	23 (17.7)
Neoplasia	37 (28.4)
Noninfectious inflammatory diseases	32 (24.6)
Miscellaneous	14 (10.7)
No diagnosis	24 (18.6)
Total	130 (100)

biopsies). The BMB was done early during the hospitalization for the workup of FUO in 55% of patients (before the 10th day of hospitalization). There were 2 BMB-associated complications (1.5%), both involving hematomas, with one occurring in a patient with a definite diagnosis of Behçet disease and the other in a patient with a diagnosis of acute leukemia. Both resolved with conservative therapy: blood transfusion and fluid therapy were necessary for 1 patient.

VALUE OF THE BONE MARROW ASPIRATE

The examination of Giemsa-stained bone marrow smears resulted in a diagnosis in 19 patients (14.6%), especially in cases of hemophagocytic syndrome, which remains only a clue but not a definite diagnosis. Indeed, in 6 cases, hemophagocytosis was observed including 2 cases of infectious diseases (*Propionibacterium acnes* bacteremia and Epstein-Barr virus primary infection), 2 observations of adult-onset Still disease, and 2 cases of hematological malignant disease (non-Hodgkin lymphoma). Finally, bone marrow aspirate resulted in specific diagnosis in 5 cases (4 cases of acute leukemia and 1 case of visceral leishmaniasis).

YIELD OF BONE MARROW CULTURE

Bone marrow cultures were performed for detecting mycobacterium infection and especially tuberculosis in all cases. However, no culture proved positive, even in the cases of suspected tuberculosis. We did not identify other pathogens in bone marrow cultures.

YIELD OF BMB

One-hundred and twenty-five patients (96.2%) presented with abnormal bone marrow findings. Indeed, findings from the bone marrow examinations showed changes that included various degrees of hypercellularity and reticuloendothelial iron storage. These histological findings were interpreted as an inflammatory modification of the marrow. Other histological features were described, such as interstitial plasmocytosis in more than 5% of the marrow in 23 cases; eosinophilia in more than 10% in 16 cases; and lymphoid nodules in 14 cases. Among these histological features, no finding represented clues for the diagnosis of the persistence of the fever. We could neither confirm a diagnosis of multiple myeloma when we observed plasmocytosis in bone marrow nor prove malignant lymphoma when we noted a lymphoid nodule.

Table 3. Bone Marrow Biopsy Results That Enabled a Diagnosis

Diagnosis	Biopsy Results, No.
Hematological malignant disease	25
Non-Hodgkin lymphoma	11
Hodgkin lymphoma	4
Acute leukemia	4
Adult T lymphoma	3
Hairy cell leukemia	1
Burkitt lymphoma	1
Multiple myeloma	1
Other diagnoses	6
Systemic mastocytosis	2
Tuberculosis	2
Granuloma	1
Visceral leishmaniasis	1

Among the 130 patients, 31 had a BMB result that enabled a diagnosis (diagnostic yield, 23.7%) (**Table 3**). In addition, in 23 observations, the pathological examination of the bone marrow was the sole exploration leading to the diagnosis of a specific condition. In patients with episodic fever, the BMB result was useful in 4 patients (8.3%). This result was significantly lower than in patients with classic FUO (8.3% vs 32.9%; $P = .002$). Table 3 gives the diagnoses established on bone marrow biopsy findings.

The histological findings in the bone marrow were contradictory with the final diagnosis in only 2 patients (1.5%). In a patient with adult-onset Still disease, the BMB result showed an aspect of T lymphoma, whereas a patient with periodic fever was thought to have a non-Hodgkin lymphoma. However, the gene rearrangement and the immunohistochemistry study findings did not show evidence of malignant hematological diseases. Seventeen patients underwent 2 or more bone marrow biopsies. The diagnosis was obtained during the second bone marrow examination in 2 cases, and the results were acute myeloid leukemia in both.

Finally, 4 types of diseases were diagnosed via BMB: hematological malignant diseases in 25 cases (80.6%), infectious diseases in 3 cases (tuberculosis in 2 cases and visceral leishmaniasis in 1) (9.6%), systemic mastocytosis in 2 cases (6.5%), and idiopathic disseminated granulomatosis in 1 case (after 4 years of follow-up, no alternative diagnosis had been established in this last patient) (3.3%).

INFLUENCE OF CORTICOSTEROIDS ON BONE MARROW EXAMINATION DURING THE WORKUP OF FUO

Even if this is not recommended, corticosteroids can be used as an empirical therapeutic test in prolonged febrile illness, especially in those who showed clinical features of temporal arteritis. We wanted to know whether corticosteroid use could hide a disease such as lymphoma or acute leukemia. We compared 2 groups, one with corticosteroid use and the other without, before the BMB was performed. Fourteen patients were receiving corticosteroids while the BMB was performed (a second

Table 4. Univariate Analysis of Patients With a Useful Bone Marrow Biopsy Result

Characteristic	BMB Contribution (n = 31)	No Contribution (n = 99)	P Value
Age, mean (range), y	56.7 (26-79)	54.5 (20-88)	.52
Sex, No.			
Male	25	77	.64
Female	19	59	
BMB date, median days after admission (range)	3.48 (1-97)	8.74 (1-450)	.65
Fever duration, median, wk	4	8	.02
Fever characteristics ^a			
CF ^b	38	94	.02
RF ^b	6	42	
Pruritus	2 (6.4)	9 (9.1)	.92
Night sweats	19 (61.3)	43 (43.4)	.07
Skin rash	3 (9.7)	22 (22.2)	.23
Superficial lymphadenopathy	7 (22.6)	10 (10.1)	.07
Splenomegaly	13 (41.9)	18 (18.1)	.007
Hepatomegaly	6 (19.4)	17 (17.2)	.78
Deep lymphadenopathy	12 (38.7)	22 (22.2)	.07

Abbreviations: BMB, bone marrow biopsy; CF, continuous fever; RF, recurrent or episodic fever.

^aNumber of patients.

^bNumber of cases.

Table 5. Baseline Biological Characteristics of Patients With BMB Contribution^a

Biological Characteristic (Reference Range)	BMB Useful	BMB Not Useful	P Value ^b
C-reactive protein (0.05-5.0 mg/L)	116 (3-292)	123 (55-342)	.81
Erythrocyte sedimentation rate, mm/h (<15 mm/h in first hour)	75.8 (30-120)	76.1 (30-122)	.60
Leukocyte count, μ L (4000-10 500/ μ L)	7670 (2000-17 000)	10 000 (3000-24 000)	.06
Eosinophil count, μ L (0-800/ μ L)	180 (0-2000)	470 (0-9400)	.47
Lymphocyte count, μ L (1000-4000/ μ L)	1500 (300-5000)	1600 (400-4700)	.17
Hemoglobin level, g/dL (13.0-17.5 g/dL)	10.3 (7.2-14.1)	11.4 (7.4-15.2)	.002
Platelet count, $\times 10^3/\mu$ L (150-400 $\times 10^3/\mu$ L)	174 (72-770)	320 (68-921)	.003
Lactate dehydrogenase, U/L (210-450 U/L)	818 (250-3200)	481 (133-1700)	.004
ALT and AST, U/L (10-65 U/L and 10-45 U/L)	49 (5-237)	23 (7-266)	.54
Alkaline phosphatases, U/L (40-129 U/L)	147 (47-734)	140 (13-671)	.90
GGT, U/L (10-65 U/L)	76 (10-267)	59 (5-442)	.26
Ferritin, ng/mL (3-300 ng/mL)	1014 (100-64 400)	376 (15-9567)	.09
β_2 -Microglobulin, mg/L (1.8-2.5 mg/L)	3.2 (1-16)	2.6 (1-10)	.01

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMB, bone marrow biopsy; GGT, γ -glutamyltransferase.

SI conversion factors: To convert C-reactive protein to nanomoles per liter, multiply by 9.524; leukocyte, eosinophil, and lymphocyte counts to $\times 10^9$, multiply by 0.001; hemoglobin to grams per liter, multiply by 10; platelets to $\times 10^9/L$, multiply by 1.0; lactate dehydrogenase, ALT, AST, alkaline phosphatases, and GGT to microkatal per liter, multiply by 0.167; and ferritin to picomoles per liter, multiply by 2.247.

^aData are given as mean (interquartile range) unless otherwise specified.

^bP values were calculated with the 2-sided χ^2 test.

biopsy in 11 cases). No significant difference was noted compared with the group of patients without corticosteroid use ($P = .58$). During the follow-up (1-5 years), only 1 patient was diagnosed as having acute myeloid leukemia.

PREDICTIVE FACTORS OF BMB CONTRIBUTION TO THE DIAGNOSIS OF FUO

Univariate Association of Risk Factors for BMB Contribution to the Diagnosis of FUO

Table 4 and **Table 5** list the clinical and biological characteristics studied as predictive factors of the yield of BMB in the workup of FUO. In an univariate analysis, the groups with and without BMB contribution did not differ significantly regarding the duration of the fever. There

were fewer patients with positive BMB results in the group with recurrent fever than in the group with continuous fever. The 2 groups did not differ for baseline erythrocyte sedimentation rate and C-reactive protein levels, although the baseline hemoglobin and platelet levels were lower in the group with positive BMB results. Lactate dehydrogenase and β_2 microglobulin were higher in the group with the useful BMB results. Only the periodicity of the fever emerged as statistically significant.

Multivariate Analysis for BMB Contribution

Five parameters (ie, splenomegaly, anemia, thrombocytopenia, lactate dehydrogenase, continuous fever) were entered in a logistic regression analysis to select variables that might predict whether BMB results were useful to the diagnosis of FUO. **Table 6** displays a multi-

Table 6. Multivariate Analysis for Predictive Factors of Bone Marrow Biopsy in the Workup of FUO

Factor	Odds Ratio (95% CI)	P Value
Splenomegaly	2.55 (0.9-7.18)	.12
Anemia, Hb <11 g/dL	3.24 (1.13-9.34)	.02
Thrombocytopenia	4.49 (1.04-9.3)	.005
Continuous fever	2.84 (1.6-12.6)	.09
LDH >450 IU/L	1.62 (0.57-4.59)	.15

Abbreviations: CI, confidence interval; Hb, hemoglobin; FUO, fever of unknown origin; LDH, lactate dehydrogenase.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10; LDH to microkatal per liter, multiply by 0.0167.

variate logistic regression analysis, which identified several risk factors that predict the probability of having a positive BMB result. The area under the receiver operating characteristic curve was 80%. Lower hemoglobin levels and lower platelet count were associated with a higher likelihood of a BMB enabling a diagnosis.

COMMENT

Despite the use of an accurate diagnostic method, the cause of FUO frequently remains obscure, and it is very difficult to edit guidelines for the care of patients with FUO.⁹ Indeed, there is no gold standard against which other diagnostic tools may be compared.⁶ Commonly, many authors evoke the use of bone marrow examination in FUO exploration.¹⁰ However, few give recommendations. In a recent review, Mourad et al^{6(p548)} wrote that "Physicians must use their discretion when determining whether there are other indications to perform a bone marrow biopsy." However, bone marrow histological techniques constitute the most commonly used diagnostic approaches.^{11,12}

Among the published cases series in immunocompetent patients, there are few data about the utility of BMB in the workup of FUO. In the 1970s, Larson et al¹³ were the first to describe the yield of BMB in the FUO diagnosis workup. This diagnostic procedure was performed in 74% of the studied patients. In 55 patients, the BMB was considered normal. In 22 cases, the biopsy findings helped to establish the diagnosis, and in 11 cases, it was the sole diagnostic tool.¹³ The yield of BMB was 14% in the study by Larson et al.¹³ The diagnosis established by the bone marrow examination was essentially hematological malignant disease. De Kleijn et al¹⁴ described the usefulness of BMB. It was performed in 49 patients (30% of the study population). Among these 49 patients, 53% had no hematological clues. As in our cases series, the yield of bone marrow examination was 20%.¹⁴ In another study, Ahmed et al¹⁵ retrospectively investigated the value of bone marrow in New York from 1993 to 2001. Both immunocompetent and immunocompromised patients were evaluated. Of the 51 BMB findings evaluated, the underlying cause of fever was detected in 8 patients (16%). Malignancy or infiltration was identified in 2 cases, granuloma in 2 cases, and mycobacterial infection in 3 cases.¹⁵ In a recent prospective study by Bleeker-Rovers et al,¹⁶ bone marrow aspiration was performed in 21 patients, but it never contributed to the di-

agnosis. The most relevant information of the study by Bleeker-Rovers et al¹⁶ was the fact that for both patients with useful BMB results, the fludeoxyglucose F 18 positron emission tomography (FDG-PET) pointed to the diagnosis. However, FDG-PET remains an expensive technique, which is not available in all countries. Even though the FDG-PET is very sensitive for detecting lymphoma, carcinoma, and osteomyelitis, it should be kept in mind that BMB is an inexpensive screening procedure that can lead to a diagnosis. The role of FDG-PET should be specified because it seems to be useful in assessing the bone marrow involvement in hematological malignant diseases, such as Hodgkin disease.¹⁷ Furthermore, many researchers reported success in using FDG-PET for localizing the source of FUO, including those caused by infections or lymphoma.¹⁸ Promising results were reported from a recent prospective study.¹⁹

A new finding of our study was the analyses of the responsiveness to steroids. We found no data about that aspect. The long-term follow-up of our patients confirmed the lack of influence of corticosteroids on the results of bone marrow examination. For instance, the bone marrow examination confirmed the diagnosis even when taking corticosteroids. We believe that other studies should confirm this point; we also think that taking corticosteroids should not lead to avoidance of performing bone marrow examination.

Our case series confirm the literature data about the very limited value of bone marrow cultures in the workup of FUO in immunocompetent patients. Indeed, we found no positive bone marrow culture. The diagnostic yield of bone marrow cultures in immunocompetent patients is very low.²⁰ We can conclude that microbiological study should not be recommended in the diagnostic workup in nonimmunocompromised patients.

Finally, even though bone marrow aspiration seems to be more easily and more quickly analyzed; BMB remains the only test capable of confirming the diagnosis of diseases such as malignant lymphoma. We should be aware of false-negative bone marrow findings in case of leukemia and particularly acute leukemia presenting as FUO.

A study limitation remains the high number of cases with a final diagnosis in the group patients with bone marrow examination. Indeed, the cause of FUO was diagnosed in 106 patients (81.4%). The proportion of undiagnosed cases (18.6%) seems low, and it remains lower than the proportion observed in more recent studies.^{21,22} However, among the 280 patients of our cohort, the cause of the fever remains obscure in 32.8%, which is similar in the last cases series.²¹ One explanation could be the long-term follow-up of our patients, since some diagnoses were done very late (2 or 3 years after the onset of the disease). The second explanation is linked to the fact that some physicians admitted diagnoses lacking confirmatory tests such as adult-onset Still disease or polymyalgia rheumatica. Moreover, long-term follow-up allowed exclusion of other diseases. Our results seem similar to those described in the older cases series, and especially, the first cohort of Petersdorf and Beeson¹ published in 1961, with 25% of the patients not having an objective diagnosis.¹³ Except for the higher preva-

lence of neoplasia, the distribution of causes of FUO in our study remains similar to those described in previous reports.²³ We voluntarily selected nonimmunocompromised patients to avoid a selection bias. Indeed, in patients with acquired immunodeficiency syndrome, BMB is known to be a useful procedure to diagnose the cause of FUO.²⁴ Benito et al⁵ reported that culture and histopathological examination enabled a diagnosis in 37.9% of cases among HIV-infected patients with FUO.

Our data confirm the older FUO cases series, and bone marrow examination should therefore be considered early in the evaluation of these patients because it may quickly lead to specific diagnosis, facilitating appropriate therapies. We should be aware of the very limited value of this test in patients with episodic fever. Furthermore, this test should be preferred in patients with thrombocytopenia or a low hemoglobin level, in whom a primary hematological disease remains suspect, confirming a correlation between hematologic finding and yield of bone marrow examination, as it was suggested in the 1970s by other authors.¹³

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