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Indications for bone marrow examinations in rheumatology

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Abstract

Hematologic involvement or hematologic malignancies are frequently encountered during the course of rheumatic diseases. Bone marrow (BM) aspiration and/or biopsy examinations may have a diagnostic role in explaining hematologic findings detected in rheumatology clinical practice. Our aim was to describe the indications for BM examinations and to share our BM aspiration/biopsy results. We analyzed 140 BM aspiration/biopsy results of patients conducted at the Department of Rheumatology from 2010 to 2018. Demographics, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) values, serum biochemistry test results including lactate dehydrogenase (LDH), organomegaly, indications for BM examinations and BM examination results for each patient, and mortality rates were recorded. Out of the 140 patients, 63.6% were female, and the median (Q1–Q3) age was 53 (39.5–65) years. One hundred fifteen (82.1%) patients were diagnosed as having primary rheumatic disease, and 25 (17.8%) were admitted due to musculoskeletal symptoms. Rheumatoid arthritis (RA) ($n=34$, [29.5%]), and systemic lupus erythematosus (SLE) ($n=21$, [18.2%]) were the most common rheumatic diseases. Cytopenia was the most common indication for BM aspiration/biopsy ($n=83$, [59.3%]). Thirty-nine (47%) of 83 patients had drug-induced cytopenia. A pathology was detected in 40 (28.5%) of the 140 BM examinations. Patients with pathologic BM results had either a hematologic malignancy ($n=38$, [95%]) or metastasis to a solid organ ($n=2$, [5%]). The group of patients with pathologic BM biopsy results had significantly higher rates of lymphadenopathy, splenomegaly, and monoclonal gammopathy compared with the group with non-pathologic results ($p=0.001$, $p=0.011$, and $p=0.023$, respectively). Likewise, LDH concentrations of those with pathologic results were higher than in patients with non-pathologic results [737 (range 577–1420) IU/L vs. 541 (range 306–840) IU/L, $p=0.019$]. In this study, cytopenia or CBC abnormalities accompanied by elevated LDH values or anemia along with increased ESR were the most common indications for BM aspiration/biopsy. Further prospective studies are needed to determine the indications of BM aspiration/biopsy and establish the parameters that predict abnormal BM results in rheumatology practice.

Keywords Bone marrow examination · Rheumatology · Cytopenia

Introduction

Bone marrow (BM) examination is an essential investigation method for the diagnosis and treatment of various blood and BM disorders [1, 2]. This interventional modality is of particular importance in the diagnosis of hematologic diseases. BM biopsy is an invasive procedure that may lead to complications including pain and bleeding at the site of biopsy, and rarely, local infection, neuropathy, and osteomyelitis [3]. BM investigation has many indications and several practice guides thereupon. BM examination is recommended in the event of unexplained anemia, abnormal red blood cell indices, cytopenia(s), cytosis(es), abnormal blood smear morphology supporting a BM pathology, suspected BM metastasis, and unexplained organomegaly, for the purpose

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of microbiologic cultures in patients with fever of unknown cause, as well as in the diagnosis, staging, and follow-up of malignant hematologic diseases [1, 3]. Other indications defined in the literature for the use of BM biopsy during the course of rheumatic diseases are monoclonal gammopathy, tumors of unknown origin, cytopenia, and bone lesions [4, 5]. Furthermore, BM assessment might be resorted to in the event of cytopenia during the course of inflammatory rheumatic disease, BM depletion due to the use of additional immunosuppressive agents, and in the determination of BM involvement (myelofibrosis) in patients with systemic lupus erythematosus (SLE) or in macrophage activation syndrome [6–11]. Moreover, hematologic malignancies may mimic rheumatic diseases, and BM biopsies collected during follow-up for a rheumatic disease may help in establishing the actual diagnosis [12].

In this paper, we aimed to share our BM aspiration/biopsy results obtained from patients with rheumatic disorders or musculoskeletal symptoms and to form possible indication sets for BM aspiration and biopsy.

Materials and methods

Patient selection

Our study included 140 patients who were followed from December 2010 to March 2018 at the Department of Rheumatology at a University Hospital where they underwent BM aspiration/biopsy. The patients were identified through the use of BM aspiration/biopsy entry codes. Patient results were obtained retrospectively from the patient files or the digital records of the hospital. We recorded the following parameters for each patient: age; sex; diagnosis of rheumatic disease or indication for hospitalization; complete blood count (CBC), erythrocyte sedimentation rate (ESR), red blood cell indices, C-reactive protein (CRP), and serum ferritin values; serum biochemistry test results including lactate dehydrogenase (LDH); serum protein electrophoresis results; presence of organomegaly (lymphadenopathy, hepatomegaly, and splenomegaly); mortality and its cause; cause of cytopenia; and the indication and result of BM aspiration/biopsy. The cytogenetic results of the patients were not included in the study.

Patients for whom data were unavailable were excluded from the study.

Description of cytopenia

A count of hemoglobin < 13 g/dL in men and hemoglobin < 12 g/dL in women was defined as anemia, and leukocyte counts of < 4000/mm^3 were defined as leucopenia. Likewise, an absolute neutrophil count of < 1500/mm^3 was defined as neutropenia, and a platelet (PLT) count of < 100,000/mm^3 was defined as thrombocytopenia. The presence of any such values was acknowledged to meet the criteria for cytopenia.

BM aspiration and biopsy examination

The patients were evaluated together with their clinical and laboratory findings, and a rheumatologist and hematologist made a joint decision to establish the indication for BM biopsy. BM aspirates and biopsies were taken from the posterior superior iliac spine in accordance with International Council for Standardization in Hematology (ICSH) guidelines [1]. BM smear preparations were evaluated by experienced hematologists. BM smear preparations were viewed under low power magnification (10×) to determine the number and cellularity of particles, the number of megakaryocytes, and to scan for clumps of abnormal cells incidence. The details of the BM smears at the back of the particles were evaluated at higher magnification (i.e., 40×, 100×). BM aspiration was evaluated in the diagnosis of hematologic diseases, as well as flow cytometric analysis in appropriate patients.

Establishment of the cause for cytopenia

Taking the clinical, laboratory, and BM findings into consideration, and also the course of disease during follow-ups for some patients, the cause of cytopenia was established. Accordingly:

(a) Cytopenia was attributed to drugs in patients who had been using suspected drugs that may result in BM suppression [e.g. methotrexate (MTX), azathioprine (AZA)] and developed cytopenia following the drug use, who had no dysplasia in BM aspiration/biopsy and who had no metastasis of hematologic or solid malignancies, and had hypocellular or normocellular BM cellularity,
(b) In the event of demonstrated fibrosis (or myelofibrosis in case of SLE) or hemophagocytosis in BM, cytopenia was attributed to the underlying disease in patients with no BM pathology, but proven disease activation irrespective of use of immunosuppressive agents,
(c) Cytopenia was attributed to malignancy in patients who had dysplasia in BM aspiration/biopsy, and also had metastasis of hematologic or solid malignancies.

The study was approved by Eskişehir Osmangazi University Ethics Committee in June 2018, with Protocol Number 25403353-0.50.99-E.64226.

Statistical analysis

Continuous data are reported as median (Q1–Q3), and categorical data are presented as percentage (%). The Shapiro–Wilk test was used to compare the conformity of the data to normal distribution. Independent sample *t* test analysis was used to compare the groups with normal distribution when there were two groups. The Mann–Whitney *U* test was used for the comparison of groups that did not have normal distribution. In the analysis of cross tables, Pearson's Chi square, Pearson's exact Chi square, Yates's Chi square, and Fisher's exact Chi square analyses were applied. To identify the direction and size of the correlation, Spearman correlation coefficients were calculated. A binary logistic regression model was used to determine the clinical and demographic variables that were independently associated with the pathologic BM results, presenting the adjusted odds ratio (OR) and confidence interval (CI) of 95%. A p value ≤ 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics 21.0 program (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Results

Out of the 140 patients subject to BM examinations between 2010 and 2018, 63.6% ($n=89$) were women and the overall median age was 53 (range 39.5–65) years. The demographics and laboratory results of the patients are provided in Table 1. One hundred fifteen (82.1%) of the 140 patients were diagnosed as having primary rheumatic disease, and 25 (17.8%) were admitted due to musculoskeletal symptoms. The five most frequent primary rheumatic diagnoses, in order of frequency, were as follows: rheumatoid arthritis (RA) 29.5% ($n=34$), SLE 18.2% ($n=21$),

Table 1 Demographics and laboratory features of 140 patients who were evaluated in the rheumatology clinic and underwent bone marrow examination

	Whole group	Patients with non-pathological BM	Patients with pathological BM	*p* value
n (%)	140 (100%)	100 (71.4%)	40 (28.5%)	–
Age, median (Q1–Q3), years	53 (39.5–65)	53 (38–67.7)	53.5 (46.2–63.7)	0.752**
Sex (F/M), *n*	89/51	66/34	23/17	0.348
Primary rheumatologic disease, *n* (%)	115 (82.1%)	86 (86%)	29 (72.5%)	0.06
Organomegaly, *n*, %				
LAP, *n* (%)	32 (22.8%)	16 (16%)	16 (40%)	0.001
HM, *n* (%)	58 (41.4%)	41 (41%)	17 (42.5%)	0.534
SM, *n* (%)	23 (16.4%)	12 (12%)	11 (27.5%)	0.014
Laboratory during BM examination				
Hb level, mean ± SD, g/dL	9.9 (8.6–11.4)	9.9 ± 2.2 (4.60–16)	10.3 ± 2.2 (6.40–17)	0.268*
WBC level, median (Q1–Q3), / mm^3	4700 (2900–8200)	4700 (2765–8600)	4200 (3000–8000)	0.829**
ANC level, median (Q1–Q3), / mm^3	2900 (1125–5775)	2900 (1000–5925)	2900 (1222–5450)	0.839**
PLT level, median (Q1–Q3), /mm^3	162,000 (71,500–285,000)	174,000 (71,000–283,000)	149,500 (73,000–290,250)	0.981**
LDH level, (normal range 135–225), median (Q1–Q3), IU/L	641 (360–902)	541 (306–840)	737 (577–1420)	0.019**
ESR level, (normal range 0–20), median (Q1–Q3), mm/h	67 (35–99)	69 (35.7–102.2)	59 (33–95.5)	0.290**
CRP level (normal range 0–0.05), median (Q1–Q3), mg/dL	3.63 (0.43–12.4)	3.98 (0.45–12.9)	2.91 (0.43–10.5)	0.790**
Ferritin level, median (Q1–Q3), ng/ml	447.8 (168.8–1249)	447.8 (131–1249)	510.4 (208.8–1264.2)	0.516**
Cytopenia during BM examination, *n* (%)	83 (59.2%)	54 (54%)	29 (72.5%)	0.526
Mortality, *n* (%)	29 (20.7%)	11 (11%)	18 (45%)	< 0.0001

F female, *M* male, *LAP* lymphadenopathy, *HM* hepatomegaly, *SM* splenomegaly, *Hb* hemoglobin, *WBC* white blood cell, *ANC* absolute neutrophil count, *PLT* platelet count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *LDH* lactate dehyrdogenase, *BM* bone marrow

*Independent sample *T*-test

**Mann–Whitney *U* Test

Behcet's disease 7.8% ($n=9$), adult-onset Still's disease (AOSD) 6.9% ($n=8$), and ankylosing spondylitis (AS) 6.9% ($n=8$). Among the patients admitted for musculoskeletal symptoms who had not been previously diagnosed with a rheumatic disease, the three most frequent reasons were joint pain 28% ($n=7$), neuropathy 8% ($n=2$), and hip pain 8% ($n=2$). The ratios of the 140 patients who underwent BM examinations are provided in Table 2.

Indications for BM aspiration/biopsy

The indications for BM aspiration/biopsy were cytopenia in 59.3% ($n=83$), anemia and elevated ESR in 25.7% ($n=36$), leukocytosis and thrombocytosis in 2.9% ($n=4$), eosinophilia in 2.9% ($n=4$), and other reasons in 9.3% ($n=13$). The indications for BM examinations in the 140 patients are listed in Table 3. The most common cause for inducing cytopenia was medications, accounting for 47% ($n=39$) of the 83 patients, in the given order: 41% ($n=16$) AZA, 38.5% ($n=15$) MTX, 7.6% ($n=3$) anti-tumor necrosis factor (anti-TNF), 5.1% ($n=2$) cyclophosphamide (CYP), 2.6% ($n=1$) sulfasalazine (SSZ), 2.6% ($n=1$) colchicine, and 2.6% ($n=1$) hydroxychloroquine (HCQ). Other causes for cytopenia were SLE in 16 (19.3%), hemophagocytic syndrome in 2 (2.4%), paroxysmal nocturnal hemoglobinuria in 1 (1.2%), and BM involvement of hematologic and solid malignancies in 25 (30.1%) patients.

Table 2 Clinical diagnosis of 140 patients who underwent bone marrow examination in the rheumatology clinic

Disease	$n=140$
Primary rheumatologic diseases, *n* (%)	115 (82.1%)
Rheumatoid arthritis	34 (24.3%)
Systemic lupus erythematosus	21 (15%)
Behçet's disease	9 (6.4%)
Adult-onset Still's disease	8 (5.7%)
Ankylosing spondylitis	8 (5.7%)
Sjögren's syndrome	8 (5.7%)
Vasculitis	4 (2.9%)
Polimyositis	4 (2.9%)
Polymyalgia rheumatica	4 (2.9%)
Scleroderma	3 (2.1%)
Familial Mediterranean fever	3 (2.1%)
Temporal arteritis	3 (2.1%)
Eosinophilic granulomatosis with polyangiitis	3 (2.1%)
Rheumatoid vasculitis	3 (2.1%)
Other causes	25 (17.8%)

Table 3 Indications for bone marrow examination of 140 patients

BM examination causes	*n* (%)
Cytopenia	83 (59.3%)
Pancytopenia	37 (44.6%)
Bicytopenia	18 (21.7%)
Anemia and thrombocytopenia	12 (8.6%)
Anemia and neutropenia	6 (4.3%)
Isolated cytopenia	28 (33.7%)
Isolated anemia	9 (6.4%)
Isolated neutropenia	14 (10%)
Isolated thrombocytopenia	5 (3.6%)
Anemia and high ESR level	36 (25.7%)
Leucocytosis and thrombocytosis	4 (2.9%)
Eosinophilia	4 (2.9%)
Others	13 (9.3%)

ESR erythrocyte sedimentation rate, *BM* bone marrow

Results of BM aspiration/biopsy

The results of BM aspiration/biopsy showed a pathology in 28.5% ($n=40$) of 140 study patients. The most common pathologic BM aspiration/biopsy results were specified as: 37.5% ($n=15$) myelodysplastic syndrome (MDS), 17.5% ($n=7$) non-Hodgkin's lymphoma (NHL), and 15% ($n=6$) acute leukemia (AL). The further details of the 40 patients with pathologic BM aspiration/biopsy are listed in Table 4.

Moreover, 22.9% ($n=32$) of patients had lymphadenopathy, 41.4% ($n=58$) had hepatomegaly, and 16.4% ($n=23$) had splenomegaly. The group of patients with pathologic BM biopsy results had significantly higher rates of lymphadenopathy, splenomegaly, and monoclonal gammopathy compared with the group with non-pathologic results ($p=0.001$, $p=0.011$, and $p=0.023$, respectively). Likewise, LDH values of patients with pathologic results were higher than in those with non-pathologic results [737 (range 577–1420) IU/L vs. 541 (range 306–840) IU/L, $p=0.019$].

Elevated LDH concentrations and splenomegaly, which were identified to be significant according to the univariate analysis, were not detected as independent variables to have a role as determinants of BM pathology when included in the logistic regression analysis (OR 0.771, 95% CI [0.104–5.724], $p=0.226$) and (OR 6.9, 95% CI [0.756–63.075], $p=0.396$), respectively.

Correlation analysis of LDH values and other laboratory parameters revealed a correlation of LDH values with PLT ($r=-0.228$, $p=0.072$) and CRP ($r=0.572$, $p=0.011$).

Mortality rates

At the time of the study, 79.3% ($n=111$) of patients were alive, and 20.7% ($n=29$) were dead. The causes of

Table 4 Characteristics of 40 patients with pathological bone marrow aspiration/biopsy

	MDS ($n=15$)	NHL ($n=7$)	Acute leukemia ($n=6$)	MM ($n=5$)	CMPN ($n=4$)	Carcinoma metastasis ($n=2$)	Primary amyloidosis ($n=1$)
Presenting symptoms	Fatigue, fever, knee pain, abdominal pain, abdominal distension, muscle pain, dyspnea, difficulty in walking, mucositis	Dyspnea, fever, rash, fatigue, back pain, hip pain, disseminated joint pain	Fever, fatigue, shoulder pain, difficulty in walking, oral aphthae, leg pain	Disseminated joint pain, lower back pain, back pain, rash, chest pain	Disseminated joint pain, dyspnea, difficulty in walking	Back pain, bone pain	Joint pain, swollen neck
BM examination indication	5 pancytopenia 2 anemia + neutropenia 2 anemia + thrombocytopenia 1 anemia + high ESR 1 neutropenia 1 anemia 1 thrombocytopenia 1 anemia + thrombocytopenia, 1 leukopenia + neutropenia	4 pancytopenia 2 anemia + high ESR 1 anemia	2 pancytopenia 2 anemia + high ESR 1 neutropenia 1anemia + thrombocytopenia	3 anemia + high ESR 2 anemia	2 leukocytosis + thrombocytosis 1 leukocytosis + thrombocytosis + polycythemia 1 anemia + neutropenia	2 anemia + high ESR	Anemia and high ESR
Diagnosis/preliminary diagnosis	3 RA 2 Behçet's disease 2 SLE 2 Scleroderma 1 Adult-onset Still's disease 1 Polymyositis 1 FMF 1 AS 1 Vasculitis 1 Rheumatoid vasculitis	2 Sjögren's syndrome, 1 Bone lesions 1 RA 1 PMR 1 Hip pain 1 Vasculitis	2 AS 1 Polymyositis 1 Difficulty in walking 1 Behcet's disease 1 Polyneuropathy	3 AS 1 Vasculitis 1 Arthritis	1 RA 1 Behcet's disease 1 Bone pain 1 APS	1 PMR 1 Psoriasis	Neuropathy
Outcome	3 Dead, 12 alive	5 Dead, 2 alive	5 Dead, 1 alive	2 Dead, 1 alive	4 Alive	2 Dead	Alive

MDS myelodysplastic syndrome, *NHL* non-Hodgkin lymphoma, *MM* multiple myeloma, *CMPN* chronic myeloproliferative neoplasia, *ESR* erythrocyte sedimentation rate, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *FMF* Familial Mediterranean fever, *AS* ankylosing spondylitis, *PMR* polymyalgia rheumatica, *APS* antiphospholipid syndrome, *BM* bone marrow

mortality were sepsis in 5.7% ($n=8$), unknown reasons in 5.7% ($n=8$), disease progression in 3.6% ($n=5$), pneumonia in 1.4% ($n=2$), invasive aspergillosis in 1.4% ($n=2$), and bleeding esophageal varices, myocardial infarct, prostate carcinoma, and respiratory failure each in 0.7% ($n=1$) of patients. Patients with pathologic BM aspiration/biopsy results had a higher mortality rate than those without a pathology ($p<0.001$).

Discussion

In our study, we assessed 140 BM aspirations/biopsies in patients with primary rheumatic diseases or musculoskeletal symptoms and showed that 28.5% of BM biopsies/aspirations had pathologic findings suggestive of hematologic or solid cancer metastasis. The most common indication for BM aspiration/biopsy was cytopenia with a rate of 59.3%, and the most common cause of cytopenia was drug-induced cytopenia at a rate of 47%.

Primary rheumatic diseases may manifest with hematologic involvements including peripheral cytopenia and BM involvement [8]. Patients with hematologic and solid malignancies that have yet to be diagnosed may visit rheumatology departments reporting musculoskeletal conditions. BM aspiration and/or biopsy may have a pivotal role with diagnostic value in the course of certain diseases.

There is a limited number of studies estimating the likelihood of a pathologic result in a BM aspiration/biopsy in rheumatic diseases or investigating parameters that require BM aspiration/biopsy. Moreover, the fact that there are methodologic differences and the retrospective design of studies has led to the heterogeneity of BM aspiration/biopsy indications [5–7, 9, 13, 14]. Loctin et al. performed BM examination in patients with health status deterioration, peripheral lymph node involvement, the presence of chronic inflammatory rheumatism and abnormal immunoglobulin levels. They also examined BM in patients with vertebral fracture and tumor of unknown origin [5]. On the other hand, Papageorgiou et al. considered "unexplained" cytopenia as an indication for BM examination [9]. Richter et al. performed BM examinations in patients with having changes in peripheral blood count including anemia, granulocytopenia (< 2500/µl), thrombocytopenia (< 100,000/µl) [6]. In our study, we formed a wide-range BM aspiration/biopsy indications including cytopenia; anemia and elevated ESR; leukocytosis and thrombocytosis in patients with musculoskeletal problems.

In Locin et al's study, BM aspiration biopsy was found to be pathologic in 16.5% of 139 patients with abnormal level of gammaglobulins. In 118 patients without gammaglobulin abnormalities, BM aspiration biopsy was found to be pathologic in 10% of patients. [5]. Papageorgiou et al. found pathologic BM aspiration/biopsy results in 28.2% of 110 patients with autoimmune disorders. Clonal hematologic diseases were detected in 77.4% patients, BM toxicity due to immunosuppressive drugs was found in 22.6% cases [9]. Richter et al. evaluated 146 BM examination in patients with rheumatic disorders because of changes in peripheral blood count. They found reactive (65.7%), nonclonal (23.9%) and clonal changes (11.6%) in the study group [6]. We detected BM abnormalities related with hematologic pathologies in 38 (27.1%) out of 140 patients. In the literature, although the most frequently detected hematologic malignancies in BM biopsy/aspiration analyses in rheumatic diseases were MDS/acute leukemia, as we found in our study, in BM biopsies/aspirations due to gammopathy, the main pathology detected was MM, as expected. In the three main studies in the literature and our study, the other hematologic pathologies beside MDS/acute leukemia were lymphoproliferative diseases, myeloproliferative neoplasia, and amyloidosis [5, 6, 9]. Although abnormal BM aspiration/biopsy results were mostly related to hematologic malignancies, in one study, solid cancers were found at a low rate. The rate of solid cancers with BM infiltration in the study of Loctin et al. was similar to that in our study [5]. The characteristics of the patients and the BM aspiration/biopsies results of our study and the three main studies in the literature are summarized in Table 5.

There is a limited number of studies estimating the likelihood of a pathologic result in a BM aspiration/biopsy in rheumatic diseases or investigating parameters that require BM aspiration/biopsy. However, Papageorgiou et al. suggested that increased serum iron levels, increased MCV and presence of monoclonal band are predefined outcomes for MDS, drug toxicity, plasma cell dyscrasia, respectively [9]. In our patients with BM pathology, elevated LDH was identified to be a significant variable according to univariate analysis, but not detected as significant based on logistic regression analysis. It is worth keeping in mind that upon a rheumatic admission for joint- and muscle-related symptoms, a diagnosis of hematologic or solid cancer might be made in the event of accompanying cytopenia, ESR elevation, and increased LDH values. Unlike other studies, we evaluated mortality rate between patients with pathological BM and non-pathological BM results. As expected, mortality rate was high in patients with pathologic BM results.

The involvement of a primary hematologic disease and BM suppression due to medication used for rheumatic disease account for a substantial indication. To this end, Richter et al. evaluated the BM of 146 patients who received HCQ 13.5%, MTX 17.3%, cyclosporine (CpA) 7.7%, mycophenolate mofetil (MMF), and leflunomide 1.9%, AZA 25%, and CYP 7.7%, where BM alterations were associated with medication in one-third of these patients [6]. In the study by Papageorgiou et al. SLE was the most common underlying

Table 5 The characteristics of the patients and the BM aspiration/biopsies results of our study and the three main studies in the literature

	Our study	Loctin et al. [5]	Richter et al. [6]	Papageorgiou et al. [9]
Patients, *n*	140	257 (BM aspiration) 79 (BM biopsy)	146	110
Age of patients, median (Q1–Q3) or (mean ± SD), years	53 (39.5-65)	Unspecified	53.5 ± 15.5	57.17 ± 14.9
Sex, %	63.6%, F	Unspecified	67.8%, F	68.1%, F
The most frequent primary rheumatologic diseases (%)	RA (29.5%) SLE (18.2%) Behçet's disease (7.8%)	Unspecified	RA (14.9%) MCTD (15.3%) SLE (11.1%)	SLE (34.5%) RA (26.3%) Vasculitis (17.2%)
The most common indications for BM aspiration/biopsy	Cytopenia—59.3% Anemia and high ESR level—25.7%	Gammaglobulin abnormalities—54% Hemogram abnormalities—24%	Peripheral blood counts abnormalities—81.7%	Hematological abnormality (unexplained cytopenia, thrombocytosis and monoclonal band)
Pathologic rates of BM examination, *n* (%)	40 (28.5%)	in BM aspiration—35 (14%) in BM biopsies—14 (18%)	52 (35.6%)	31 (28.2%)
The results of pathologic BM examination				
The ratios of hematological diseases, %	Hematologic—95%	Hematologic—90%	Hematologic (clonal)—32.6%	Hematologic—77.4%
The ratios of solid malignancies, %	Solid—5%	Solid—7%	Solid—none	Solid—none
Others	None	Tuberculous osteomyelitis—3%	Non-clonal—67.4%[a]	BM toxicity—22.6%
The most common hematologic diseases in BM examination, *n*	15 MDS 7 NHL 6 AL 5 MM 4 CMPN 1 Primary amyloidosis	12 MM 8 NHL 6 MDS 4 CLL 3 WM 2 CMML 1 AL 1 HCL 1 PMF 1 Primary amyloidosis	9 MDS/AL 5 NHL 3 CMPN	11 MDS 4 MGUS 4 NHL 2 MM 2 CLL 1 CMPN

SD standard deviation, *BM* bone marrow, *F* female, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus *MCTD* mixed connective tissue disease, *ESR* erythrocyte sedimentation rate, *MDS* myelodysplastic syndrome, *NHL* non-Hodgkin lymphoma, *AL* acute leukemia, *MM* multiple myeloma, *CMPN* chronic myeloproliferative neoplasia, *CLL* chronic lymphocytic leukemia, *WM* Waldenström macroglobulinemia, *CMML* chronic myelomonocytic leukemia, *HCL* hairy cell leukemia, *PMF* primary myelofibrosis, *MGUS* monoclonal gammopathy of undetermined significance

[a]26.7% *MGUS*, 11.4% immune thrombocytopenia, 62.9% anemia of inflammation

disease, anemia was the most frequent indication for BM examination, and more than half of the patients were on immunosuppressive treatment (most commonly using MTX followed by CYP, anti-TNF, rituximab, AZA, CpA, and MMF) and drug-induced toxicity was at a rate of 6.4% [9]. In our series, on the other hand, the most important reason of BM aspiration/biopsy was pancytopenia, which most frequently occurred due to drug-induced toxicity. We found drug-induced toxicity at a level of 27.9%, which is higher than in the literature. The drug that most frequently resulted in BM toxicity was MTX in the study by Papageorgiou et al. whereas it was AZA and MTX in the present study [9]. Drug-induced cytopenia results either from the suppression of BM progenitor cells directly by the drug, leading to attenuated production or from escalated cell destruction due to the immune mechanism induced by drug-related autoantibodies. Laboratory testing for drug-dependent antibodies is rarely performed because of the complexity and low sensitivity of tests currently in use [15]. Accordingly, it is challenging to establish the definite cause of drug-induced cytopenia.

The limitations of our study include its retrospective design, the relatively small sample size, and the lack of cytogenetic analysis. The heterogeneity of our patient group (composed of novice patients as well as follow-up patients on drug treatment) is another limitation. Moreover, in certain

rheumatic diseases for which the manifestation includes cytopenia, SLE being in first place, it is more likely that a BM biopsy is performed, which may have caused bias in our study because the patients with SLE and RA in our study were those with the highest incidence of BM investigations.

Conclusions

Based on the results of our study, the most common indications for BM aspiration/biopsy in our clinical practice were included cytopenia or abnormal CBC findings along with increased LDH values, and unexplained persistent anemia along with increased ESR levels. Although we could not find any predictors for pathological BM results, organomegaly and increased LDH levels were more commonly observed in patients with having abnormal BM results. Further prospective studies are needed to determine the indications of BM aspiration/biopsy and establish the parameters that predict abnormal BM results in rheumatology practice.

Author contributions HUT and DUC designed, collected the data and analyzed the results, HUT, DUC and CK wrote the manuscript, critically reviewed the manuscript and wrote the final version. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was not obtained from the patients since ethics committee did not ask for it in such studies processing medical records anonymously.

Informed consent Written informed consent was not obtained from the patients since ethics committee did not ask for it in such studies processing medical records anonymously.

References

1. Lee SH, Erber WN, Porwit A, Tomonaga M, Peterson LC (2008) ICSH guidelines for the standardizations of bone marrow specimens and reports. Int Jnl Lab Hem 30:349–364
2. Focosi D (2010) Bone marrow aspiration and biopsy. N Engl J Med 362:182–183
3. Bain BJ (2006) Morbidity associated with bone marrow aspiration and trephine biopsy: a review of UK data for 2004. Haematologica 91:1293–1294
4. Garton MJ, Keir G, Dickie A, Steven M, Rennie JA (2006) Prevalence and long-term significance of paraproteinaemia in rheumatoid arthritis. Rheumatology 45:355–356
5. Loctin A, Bailly F, Laroche D, Tavernier C, Maillefert JF, Ornetti P (2013) Clinical interest of bone marrow aspiration in rheumatology: a practice-based observational study of 257 bone marrow aspirations. Clin Rheumatol 32:115–121
6. Richter JG, Gossen P, Germing U, Blum S, Hildebrandt B, Braunstein S, Huscher D, Schneider M (2009) Rationale for bone marrow examination in patients with inflammatory rheumatic diseases. Wen Klin Wochenschr 121:690–699
7. Hunt KE, Salama ME, Sever CE, Foucar K (2013) Bone marrow examination for unexplained cytopenias reveals nonspesific findings patients with collagen vascular disease. Arch Pathol Lab Med 137:948–954
8. Üsküdar Cansu D, Üsküdar Teke H, Işiksoy S, Korkmaz C (2018) Bone marrow as a target organ of systemic lupus erythematosus: analysis of cases with myelofibrosis. Int J Rheum Dis 21:1049–1059
9. Papageorgiou A, Ziakas PD, Tzioufas AG, Voulgarelis M (2013) Indications for bone marrow examination in autoimmune disorders with concurrent haematologic alterations. Clin Exp Rheumatol 31:76–83
10. Grom AA, Horne A, De Benedetti F (2016) Macrophage activation syndrome in the era of biologic therapy. Nat Rev Rheumatol 12:259–268
11. Esatoglu SN, Hatemi G, Salihoglu A, Hatemi I, Soysal T, Celik AF (2015) A reappraisal of the association between Behçet's disease, myelodysplastic syndrome and the presence of trisomy 8: a systematic literature review. Clin Exp Rheumatol 33(6 Suppl 94):S145–S151
12. Bornstein G, Furie N, Perel N, Ben-Zvi I, Grossman C (2018) Hematological malignancies mimicking rheumatic syndromes: case series and review of the literature. Rheumatol Int 38:1743–1749
13. Kim HA, Kwon JE, Yim H, Suh CH, Jung JY, Han JH (2015) The pathologic findings of skin, lymph node, liver, and bone marrow in patients with adult-onset still disease: a comprehensive analysis of 40 cases. Medicine (Baltimore) 94:e787
14. Rosenthal NS, Farhi DC (1989) Bone marrow findings in connective tissue disease. Am J Clin Pathol 92:650–654
15. Curtis BR (2017) Non-chemotherapy drug-induced neutropenia: key points to manage the challenges. Hematology Am Soc Hematol Educ Program. 2017:187–193