A multicenter retrospective study defining the clinical and hematological manifestations of brucellosis and pancytopenia in a large series: Hematological malignancies, the unusual cause of pancytopenia in patients with brucellosis

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The aim of the study is to review the clinical manifestations and the hematological findings of brucellosis and pancytopenia, with or without hematological malignancies. The records of 202 patients with brucellosis were evaluated retrospectively. Among these cases of brucellosis seen in a 6 year period between April 1999 and June 2005, 30 patients with pancytopenia were identified. The most common manifestation was fever, followed by weight loss, anorexia, malaise, arthralgia, and hepatosplenomegaly. Bone marrow biopsies revealed hypercellularity or normocellularity. The most common findings in the bone marrow evaluation were histiocytic hemophagocytosis and granulomas. Among all cases, we diagnosed 5 hematological malignancies (1 acute myelogenous leukemia, 2 acute lymphoblastic leukemia, and 2 multiple myeloma) concurrently with brucellosis. The clinical symptoms and findings were similar in patients with and without malignancies. In cases with malignancies, the bone marrow biopsy revealed predominant primary disease involvement. Significant increases in ESR and CRP, severe anemia and thrombocytopenia were observed in patients with malignancies. Peripheral blood counts in patients without malignancies returned to normal after antibiotic treatment for brucellosis. However, pancytopenia in two patients with malignancies did not recover because of primary resistant disease. We conclude that while histiocytic hemophagocytosis may be considered as a major cause of pancytopenia, leukemic infiltration can also be an extreme and unusual cause of pancytopenia in patients in whom brucellosis was concurrently diagnosed with hematological malignancies. Am. J. Hematol. 83:334–339, 2008. © 2007 Wiley-Liss, Inc.

Introduction

Brucellosis is a zoonotic infection existing worldwide, with predominance in central Asia and some developing countries. The disease is also present, in varying trends, in European countries and the USA [1]. Brucellosis is caused by small, fastidious gram-negative coccobacilli of the genus Brucella. *B. melitensis* is the most invasive and causes the most severe disease. The infection because of *B. Melitensis* is a common disease in Turkey [2], and humans are commonly infected through ingestion of raw milk, cheese, meat, or through direct contact with infected animals, products of conception, or animal excreta [3].

Human brucellosis has a wide clinical spectrum [4]. Hence, it presents various diagnostic difficulties as it mimics many other diseases. The disease also produces a variety of nonspecific hematological abnormalities. Bone marrow and the spleen are commonly involved, and such involvement may result in a hypoplastic pattern on the peripheral blood smear [5,6]. Hematological complications of mild anemia and leukopenia have been frequently associated with acute brucellosis, but pancytopenia and thrombocytopenia are less frequently encountered [7,8].

Additionally, bone marrow involvement because of the concurrent presentation of malignant disease with brucellosis rarely leads to pancytopenia [9,10]. Despite the fact that pancytopenia associated with brucellosis has been well described in the medical literature, malignant diseases in association with pancytopenia and brucellosis are extremely rare, even in reports from the Mediterranean countries where brucellosis is endemic. The aim of this study was to review the clinical manifestations and the hematological findings in a large series of cases with brucellosis and pancytopenia, and to describe five patients infected with *Brucella* presenting with pancytopenia, who were diagnosed with concurrent hematological malignancies.

Results

Patients' general characteristics and clinical findings

The study takes into account 202 adult patients, who were hospitalized with the diagnosis of brucellosis. Of those, 30 patients (14.9%), 12 males and 18 females, with ages ranging from 17 to 76 (median 44.5) years, had pancytopenia at the time of diagnosis. All patients had been previously healthy with no history of hematological disorders. The general characteristics of these 30 patients with brucellosis and pancytopenia are summarized in Table I.

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Received for publication 8 February 2006; Revised 18 July 2007; Accepted 13 September 2007

Am. J. Hematol. 83:334–339, 2008.

Published online 10 December 2007 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ajh.21098

TABLE I. General Characteristics and Clinical Findings of 30 Patients with Brusellosis and Pancytopenia

Patients' characteristics	Patients	%
Sex (male/female)	12/18	40/60
Median patient age (range), year	44.5 (17–76)	
Consumption of raw milk (or products), or contact with domestic animals	22	73.3
Living in rural and mountainous areas	26	86.7
Family history	7	23.3
Time elapsed between the presumed exposure and the onset of illness	Unknown	
Symptoms/signs		
Fever	30	100.0
Weight loss	23	76.7
Anorexia	22	73.3
Malaise	22	73.3
Arthralgia	20	66.7
Splenomegaly	19	63.3
Hepatomegaly	19	63.3
Arthritis	17	56.7
Headache	15	50
Sweating	14	46.7
Myalgia	13	43.3
Petechiae and purpuras	13	43.3
Lymphadenopathy	12	40
Gastro-intestinal symptoms	11	36.7
Back pain	3	10
Epistaxis	3	10
Cardiac manifestations	3	10
Jaundice	2	6.7
Abscess	1	3.3
Hematuria	1	3.3

The clinical findings observed in these 30 patients have been presented in Table I. Nonspesific manifestations were predominant in the patients. Fever was present in all the patients. The other common symptoms and findings were weight loss, anorexia, malaise, arthralgia, and hepatosplenomegaly. The size of the spleen did not correlate with the degree of pancytopenia in patients who had hepatosplenomegaly.

Interestingly, among these 30 cases, we diagnosed 5 concurrent hematological malignancies. One patient had acute myelogenous leukemia (AML), 2 had acute lymphoblastic leukemia (ALL), and the remaining 2 patients had multiple myeloma (MM). These patients did not have any specific clinical symptoms and/or findings related with their malignant disease (Table IV). They were admitted to our hematology–oncology departments in order to undergo investigation towards the etiology of pancytopenia and fever, as well as most of the other aforementioned cases. The peripheral blood smear of the patients with acute leukemia revealed pancytopenia and rare blasts (myeloblast or lenfoblast). Only rulo formations and pancytopenia were observed in the peripheral blood smear of multiple myeloma patients. Hence, bone marrow aspiration and biopsy were planned. Finally, accurate diagnoses of acute leukemia and multiple myeloma in these patients were established by immunohistochemistry, flow cytometry, and other special tests (serum and urine immune electrophoresis, cytogenetic analysis etc.). On the other hand, the diagnosis of acute brucellosis was established incidentally by serum agglutination tests, and blood and bone marrow cultures that were performed on admission for the differential diagnosis of pancytopenia. The general characteristics, clinical and laboratory manifestations of these 5 patients are shown in Table II.

Agglutination titers and blood and bone marrow cultures

The diagnosis of brucellosis in all pancytopenic patients was confirmed by the standard tube agglutination test. The titers were 1:160 in 4 patients (13.3%), 1:320 in 4 patients (13.3%), 1:640 in 5 patients (16.7%), 1:1,280 in 9 patients (30%) and 1:2,560 in 8 patients (26.7%). Blood and bone marrow cultures for *Bucella spp*. were positive in 20 patients (%66.7), bone marrow cultures were positive in 6 patients (20%), who displayed negative blood cultures, and blood cultures were positive in 3 patients (10%), who displayed negative bone marrow cultures. The remaining one patient showed only a positive agglutination test at a titer of 1:1,280, but negative blood and bone marrow cultures.

The results of the standard tube agglutination tests and blood-bone marrow cultures have been demonstrated in Table II for patients with acute leukemias and multiple myelomas. Bone marrow cultures were positive in all patients with malignancies and agglutination titers were generally high except for the AML patient. Special stains and cultures of the bone marrow for acid-fast bacilli and fungi revealed

TABLE II. General Characteristics, Clinical and Laboratory Manifestations of 5 Brucellosis Patients with Concomitant Hematological Malignancies

Patients	Diagnosis	Fever	Sweating	Anorexia	Weight loss	Petechiae-purpura	Back pain	Lympadenopathy and Hepatosplenomegaly
1	AML	+	+	+	+	+	−	+
2	ALL	+	+	+	+	+	−	+
3	ALL	+	+	+	+	+	−	+
4	MM	+	+	+	−	−	+	−
5	MM	+	+	+	+	+	+	−

Patients	Diagnosis	Subtype	Age	Sex	STA	ESR	CRP	Blood culture	Bone marrow culture
1	AML	M4	58	Female	1:160	90	74	Positive	Positive
2	ALL	L2	39	Female	1:2,560	105	79	Negative	Positive
3	ALL	L2	40	Female	1:2,560	95	40	Positive	Positive
4	MM	IgG kappa	76	Female	1:2,560	105	70	Positive	Positive
5	MM	IgA kappa	63	Male	1:2,560	103	40	Positive	Positive

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma; +, present; −, absent; STA, standard tube agglutination; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; MM, multiple myeloma.

TABLE III. The Results of Initial Peripheral Blood Cell Count and Some Laboratory Tests in 30 Brucellosis Patients with and Without Hematological Malignancies

Parameters	Patients	Mean ± SD	%95 CI	Median (Min-Max)	Mann–Whitney *Z* value	*P*-value
Hb	WM	10.58 ± 1.67	9.89–11.27	10.20 (8–13.4)	3.09	=0.001
	M	7.56 ± 1.43	5.78–9.34	7.4 (6–9.9)		
	Total	10.08 ± 1.98	9.34–10.82	10.15 (6–13.4)		
WBC	WM	3,172 ± 358.10	3024.18–3319.81	3,200 (2,600–3,900)	1.26	=0.22
	M	2,260 ± 1361.25	569.78–3950.21	3,000 (500–3,500)		
	Total	3,020 ± 693.69	2760.97–3279.03	3,200 (500–3,900)		
N	WM	1,915 ± 505.38	1706.98–2124.21	2,000 (800–3,000)	1.75	=0.08
	M	1,150 ± 959.16	−40.96–2340	1,500 (50–2,000)		
	Total	1,788 ± 649.99	1545.28–2030.71	2,000 (50–3,000)		
L	WM	1,074 ± 378.22	918.28–1230.52	1,000 (400–2,000)	0.50	=0.52
	M	930 ± 380.13	458.00–1401.99	900 (450–1500)		
	Total	1,050 ± 375.92	909.96–1190.70	1,000 (400–2,000)		
Plt	WM	95,560 ± 33,570	81,702–109,417	108,000 (17,000–134,000)	2.90	=0.002
	M	33,600 ± 21,384	7,047–60,152	27,000 (17,000–70,000)		
	Total	85,233 ± 39,336	70,544–99,921	93,500 (17,000–134,000)		
CRP	WM	36.26 ± 39.22	20.06–52.44	24 (0.30–173)	2.14	=0.03
	M	60.60 ± 19.07	36.91–84.28	70 (40–79)		
	Total	40.31 ± 37.53	26.30–54.33	34.5 (0.30–173)		
Sed	WM	46.84 ± 30.78	34.14–59.54	50 (4–100)	3.29	<0.001
	M	99.60 ± 6.77	91.19–108.00	103 (90–105)		
	Total	55.63 ± 34.50	42.75–68.52	59 (4–105)		

WM, patients without malignancies; M, patients with malignancies.

negative results in all patients with brucellosis and pancytopenia.

The results of peripheral blood cell counts and some laboratory tests

The results of median and mean values of the initial peripheral blood cell count and some laboratory values in 30 patients have been displayed in the Table III. While the median value of hemoglobin concentration and platelet counts were lower, the values of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were significantly higher in the patients with malignancies (M), when compared with the patients without malignancies (WM) ($P = 0.001$, $P = 0.002$, $P = 0.03$, and $P < 0.001$; respectively). The reticulocyte counts were normal in all but one patient who had thrombotic microangiopathy.

Examination of bone marrow aspirations and biopsies

The results of bone marrow aspirations and biopsies of 30 patients are shown in Table IV. Examinations of the bone marrow biopsies mostly revealed hypercellularity. In majority of the bone marrows of the cases, histiocytic proliferation, mild to severe hemophagocytosis, and granulomatous lesions were detected (Figs. 1 and 2). Granulomas were small in size and consisted mainly of aggregates of epitheloid cells and lymphocytes (Fig. 2). The multinucleated giant cells of Langhans or foreign body type were not observed in any of the biopsies. There was no caseation in any of the granulomatous lesions. Neither malaria pigment nor other evidence of parasitic infestation was found.

In three cases with acute leukemia and two cases with multiple myeloma, bone marrow biopsies were hipercellular and showed the predominantly primary disease involvement (Fig. 1). Neither hemophagocytosis nor granulomatous lesions were present.

Treatment and outcome

Patients without malignancies were successfully treated with a combination of doxycycline and rifampicin or streptomycin for 6–8 weeks. The pancytopenia in these patients regressed completely and their peripheral blood counts returned to normal after treatment. In this group, 3 of the patients presented with a relapse in the 3rd, 4th, and the 7th months after treatment had ended.

All patients with hematological malignancies were successfully treated with a combination of doxycycline and rifampicin given over 6 weeks. Among patients with malignancies, no relapse occurred and the blood and bone marrow cultures, in addition to the agglutination tests were negative for brucella. However, pancytopenia in a patient with ALL (patient 3) and in another with MM (patient 4) did not regress and these patients died due to resistant disease during treatment. The remaining patients were in complete remission, and the follow-ups still continued.

Discussion

Patients, who are hospitalized because of pancytopenia with the provisional diagnoses of hematological–oncological diseases, are still found to have underlying infectious etiologies such as brucellosis. We have previously reported inter-

TABLE IV. The Results of Bone Marrow Aspiration and Biopsies of 30 Patients with Brusellosis and Pancytopenia

Bone marrow aspiration and biopsy	Patients	%
Cellularity		
Hypercellular	23	76.7
Normocellular	7	23.3
Hypocellular	–	–
Findings		
Haemophagocytosis	15	50.0
Mild	5	16.7
Severe	10	33.3
Histiocytic hyperplasia	18	60.0
Granulamatous lesions	10	33.3
Infiltration of blast cell	3	10.0
Infiltration of myeloma cells	2	6.7
Erythroid hyperplasia	1	3.3

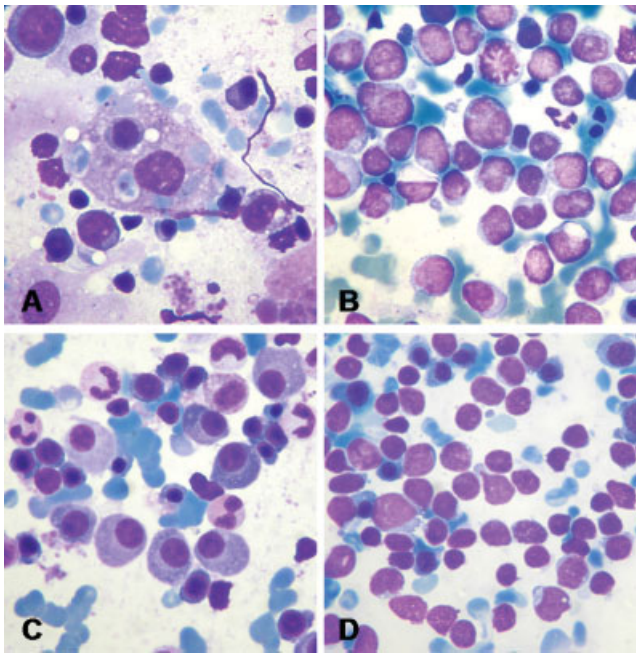

Figure 1. (A) A bone marrow smear demonstrating hemophagocytosis by a large histiocyte in a patient with brucellosis (Giemsa stain ×1,000). (B) Acute myelomonocytic leukemia showing 90% blasts in the bone marrow (BM) aspirate smear (patient 1). (Giemza stain ×1,000) (C) A bone marrow smear revealing myeloma cells (patient 4) (Giemsa stain ×1,000). (D) ALL in patient 2 (Giemza stain ×1,000). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

esting cases of brucellosis in patients presenting with either initial hematological manifestations or unexplained fever that were referred to our university hospitals' hematology–oncology clinics [11–16]. Several data have been reported on the frequency and diversity of hematological abnormalities occurring in brucellosis [6,7,17]. In the published series, the incidence of pancytopenia with brucellosis varies from 3 to 21% [5,17,18]. In this study, 202 patients with brucellosis were investigated and pancytopenia was detected in 30 (14.9%). This result is consistent with previous reports on the incidence of pancytopenia in brucellosis.

The pathogenesis of pancytopenia in brucellosis has not been clearly understood, but it seems to be multifactorial. Several possible mechanisms have been suggested for pancytopenia caused by brucellosis, such as hemophagocytosis, hypersplenism, bone marrow granulomas, bone marrow hypoplasia, and immune destruction [17–21].

Hemophagocytosis has been observed in many infections, mainly viral, but it has also been seen in bacterial, fungal, and parasitic infections [22]. In over half of our patients, bone marrow aspirations and biopsies revealed histiocytic hyperplasia with prominent phagocytosis of erythrocytes, leukocytes, platelets and their precursors, representing a benign form of reactive histiocytosis. Additionally, in early stages, the bone marrow appears hypercellular without any typical diagnostic findings, and hemophagocytosis is usually not evident. Therefore, the actual rate of hemophagocytosis in our series may in effect be higher than could be found. In contrast to the malignant histiocytosis in which the disease runs a rapidly deteriorating course [23], the *Brucella*-associated histiocytic hemophagocytosis is potentially reversible [24]. Similarly, all our patients completely recovered, and following antibiotic therapy, the hematological abnormalities reverted to normal values. Histiocytic hemophagocytosis may be primarily responsible for pancytopenia in our patients with brucellosis.

The presence of bone marrow granulomas has been demonstrated in brucellosis [17,25,26]. The *Brucella*-associated granulomas tend to be small and poorly defined, and caseation necrosis never occurs, as demonstrated in our study. The formation of these granulomas may reflect an effective defense mechanism against brucella organisms in view of their capability of intracellular survival. Generally, they are best detected in histological sections. Hence, in our study, noncaseating granulomas were observed in the bone marrow biopsies of 33.3% of the patients.

In previous reports, hypersplenism has been implicated in patients with pancytopenia associated with brucellosis [21,27]. Since seven patients in this study showed splenomegaly, hypersplenism cannot be excluded as the cause of pancytopenia in these patients. However, splenomegaly was not huge and reticulocyte counts were normal in all but one patient. Furthermore, the hematological abnormalities resolved before resolution of splenomegaly. Therefore, it seems that hypersplenism was not the major cause of pancytopenia in our series. The role of bone marrow hypoplasia in the pathogenesis of pancytopenia has rarely been reported in patients with brucellosis [28]. In our series, the increased and normal cellularity of bone marrow in patients indicated that bone marrow failure was not the cause of pancytopenia.

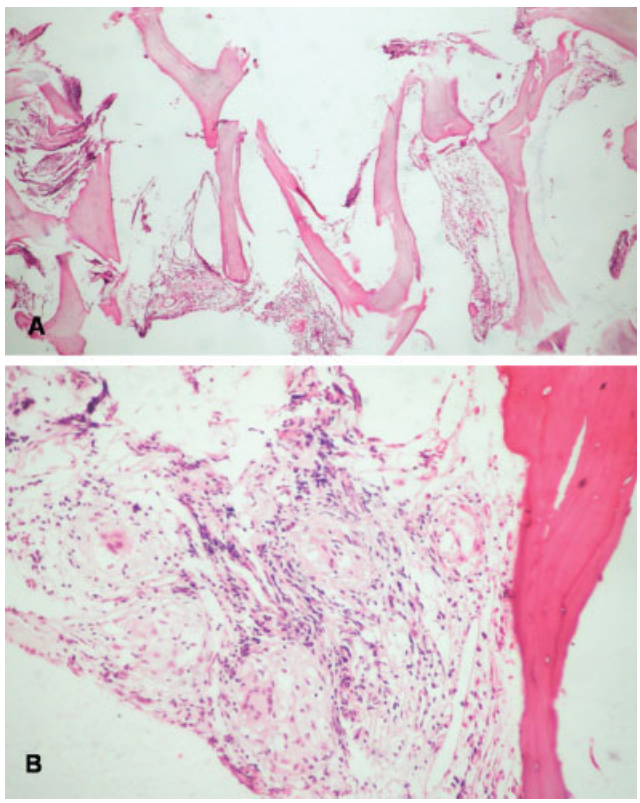

Figure 2. (A) Light microscopic examination of the trephine biopsy showing bone trabecula and granulomatous inflammation (Hematoxylin-eosin, ×40). (B) Small-medium sized noncaseating granulomas were seen at higher magnification (Hematoxylin-eosin, ×200). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

We diagnosed five patients with hematological malignancies (16.7%) including ALL, MM, and AML within all the cases with brucellosis and pancytopenia. Our university hospitals are the main referral centers for complicated patients; hence, this percentage may be very high. In the medical literature, solid tumors or hematological malignancies associated with brucellosis are extremely rare. Previously, multiple myelomas, hepatocellular carcinoma, sinus histiocytosis with massive lymphadenopathy, hairy cell leukemia, Hodgkin's disease, and non-Hodgkin lymphoma have been reported in association with brucellosis [9,10,29–32]. Because of the concomitant immunosupression of a normal antibody response in these malignancy patients, anti-brucella titers may be of no value, and culture of the organism may be necessary to make a diagnosis. Moreover, brucellosis may be responsible for deterioration and death in such cases [32]. In our cases, blood and/or marrow cultures were positive in all patients and no deterioration or death was observed because of brucellosis.

In the study, the clinical symptoms and findings were similar between the patients with and without malignancies. However, there were some differences in the laboratory results of these two groups of patients. Elevation in ESR and CRP, and severe anemia and thrombocytopenia were more marked in the patients with malignancies. On the other hand, it may be rather assertive to make a comment regarding the differential diagnosis with hematological malignancies according to the laboratory parameters in those patients with brucellosis and pancytopenia. We showed hypercellularity and infiltration with malignant cells in the bone marrow examinations of these cases. Neither hemophagocytosis nor granulomatous lesions were present. Therefore, leukemic infiltration of the bone marrow may be considered to be responsible for the pancytopenia in these five patients.

The World Health Organization has recommended oral doxycycline 200 mg/day, rifampin 600 mg/day for 6 weeks as standard therapy for brucellosis with low rate of recurrence. Antimicrobial therapy shortens the duration of the illness and reduces the incidence of complications in brucellosis. However, there are no standard recommendations for treatment alternatives and duration of therapy in immunocompromised patients.

In the literature, there is no study dealing with the role of Brucella infections in the development of leukemia in humans. However, the increase in the absolute number of splenic cells in mice infected with the Rauscher leukemia virus and brucella was initially caused by lymphoid tissue reaction to brucella rather than development of leukemia in mice [33]. It is difficult to distinguish concomitant occurrence of brucellosis and hematological malignancies from facilitated effects or coincidental events.

In conclusion, the hematological findings and treatment results in our patients showed that the differential diagnosis should include brucellosis in patients presenting with fever and pancytopenia, especially in regions where brucellosis is endemic. The pathogenesis of pancytopenia is not clear, but it seems that more than one mechanism is responsible. According to our results, histiocytic hemophagocytosis may be a major cause of pancytopenia in patients with brucellosis. On the other hand, leukemic infiltration could be an extreme and unusual cause of pancytopenia, especially in patients with brucellosis, who were diagnosed as having concomitant hematological malignancies. So, in endemic regions for the disease, a bone marrow aspiration and/or biopsy should be considered, both for the determination of the cause of pancytopenia and to eliminate any other diseases that may be a cause of pancytopenia, even if brucellosis is accurately diagnosed in these patients. However, routine screening of patients with leukemia by serological tests is questionable due to the low sensitivity of the agglutination tests in the endemic areas. Finally, in patients with brucellosis and hematological malignancy, the simultaneous treatment of infection and malignant disease may be considered to decrease the morbidity and mortality.

Patients and Methods

Records of 202 adult patients with brucellosis in Erciyes University Hospital, Pamukkale University Hospital, and Gaziantep University Hospital, were studied retrospectively. 30 patients with pancytopenia were identified among these cases of brucellosis seen in a 6 year period between April 1999 and June 2005.

All patients provided a detailed history and underwent a general physical examination. Blood samples were obtained from each patient for complete blood count, *Brucella* serology and *Brucella* cultures. Because of the fact that *brucella* infection with pancytopenia may mimic malignancy in adults, examination of the bone marrow aspirates was performed at the initial presentation of the disease (prior to the diagnosis) for differential diagnosis of pancytopenia. Bone marrow aspiration was not performed on brucellosis patients without pancytopenia. Bone marrow aspiration and obtaining of the biopsy specimen took place following acquiring informed consent, from the iliac crest of all 30 patients for microbiological culture, cytological study and histopathological examination.

Diagnosis of brucellosis was made on the basis of a clinical picture compatible with the disease, together with Brucella agglutination titers of $\geq$1:160, or isolation of *Brucella* organism from blood and/or bone marrow [3,7].

Prior to initiation of the specific treatment, only the initial hematological findings were included in the present study. White blood cell counts, differential counts, and hemoglobin levels were considered abnormal according to the established reference values in healthy individuals [34]. Pancytopenia was defined as the presence of leukopenia (WBC $<$ 4.0×10^9/L,), anemia (Hb $<$ 12 g/dL in women; Hb $<$ 14 g/dL in men), and thrombocytopenia (plt $<$ 150×10^9/L) in the same patient.

For treatment of brucellosis, the preferred antibiotic regimen consisting of doxycycline, in addition to rifampicin or streptomycin was administered for a minimum of 6 weeks. Follow-up was performed according to the individual response.

Statistics

Thirty patients with brucellosis and pancytopenia were grouped into two categories according to the presence or absence of hematological malignancy. The mean values of peripheral blood cell counts, serum CRP, and ESRs of the two groups were compared using the Mann–Whitney *U* test. A *P* value of $\leq$0.05 was considered statistically significant.

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