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Acute pancreatitis and low ascites-serum albumin gradient ascites caused by Brucellosis

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ABSTRACT

Objective: Brucellosis is a zoonotic disease seen widely around the world. Although many aspects and treatment of this disease is well known, peritoneal involvement and ascites is not well established so far.

Material and Methods: This study retrospectively enrolled 346 adult patients (aged >17 years) with acute Brucellosis attending Hepatology Clinic, Van Yuzuncu Yil University, between April 2013 and May 2016. Characteristics of those with and without ascites were analyzed using Pearson correlation coefficients and Chi-Square test in SPSS software system.

Results: Of the 346 cases, 20 (5, 7%) had ascites. Those with ascites had significantly higher transaminase, cholestatic enzyme and amylase levels compared to those without ascites.

Conclusions: We conclude that acute Brucella infection can lead to a unique low gradient ascites probably resulting from pancreatic leakage followed by peritoneal accumulation of serum proteins.

Keywords: Brucellosis, ascites, pancreatitis

INTRODUCTION

Various diseases can cause ascites, defined as accumulation of fluid within peritoneal space. Ascites is classified into two major groups depending on presence of portal hypertension. Calculation of serum ascites albumin gradient (SAAG) is the key to discriminate causes of non-portal hypertensive ascites (1). SAAG is calculated by extraction of ascites albumin from serum albumin. A value lower than 1.1 gr/dl indicates a non-portal hypertensive cause including peritoneal carcinomatosis, infectious peritonitis and other peritoneal diseases. Low gradient ascites has also higher levels of total protein levels compared to high gradient (portal hypertensive type) ascites (2). Brucellosis is a zoonotic disease caused by Brucella species B. abortus, B. melitensis, B. suis and B. canis (Table-1). Brucellosis could be viewed as an extinct disease in developed countries, but the prevalence of Brucellosis in many developing areas of the world is still high (3). Brucellae are small, gram-negative, non-motile, aerobic coccobacilli. Goat, sheep and cow are the reservoir of infection, and animal products including milk, cheese and butter can act as a bridge of transmission from animal to human. The disease is an emerging problem in Mediterranean Basin as well as elsewhere in the developing world (4). The disease has many clinical manifestations and complications including hepatitis, hepatic granulomas, peritonitis, sacroiliitis, spondylitis, meningitides, epididymoorchitis, vasculitis, bone marrow involvement (figure), pneumonia and pancreatitis. On the other hand, peritoneal involvement of the disease has rarely been reported and limited into a few case reports (5-9). Despite a well-established association of ascites with acute bacterial peritonitis, there are few data regarding the prevalence and nature of ascites in patients with acute Brucellosis. Thus, the aim of the current study is to clarify of some aspects of Brucellosis related ascites.

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MATERIAL and METHODS

The study retrospectively enrolled 346 adult patients (aged >17 years) with acute Brucellosis attending Hepatology Clinic, Van Yuzuncu Yil University, between April 2013 and May 2016. Twenty of the patients diagnosed with brucella had ascites in the abdomen. The approval of the ethical committee required to conduct the study was obtained from the Van Yuzuncu Yil University Faculty of Medicine, Clinical Research Ethics Committee(Non-invasive Clinical Research Ethics; Approved on 21.02.2020 with the 2020/02-03 number). Patients with liver cirrhosis, cardiac failure, chronic viral hepatitis, metabolic liver diseases, chronic renal failure and insufficient follow-up data were excluded from the study. Brucellosis was diagnosed by the presence of appropriate clinical signs and symptoms and at least one of these criteria: (i) positive standard tube agglutination test (STA) (a titer higher than 1/160); (ii) positive Coombs test (titer 1/160); (iii) isolation of Brucella organisms from cultures of blood, bone marrow, cerebrospinal fluid, other sterile sites, or tissue samples. Clinical and biochemical data were obtained from medical records. The diagnosis of Brucellosis-related ascites was made by both abdominal ultrasonography and computed tomography. Diagnostic paracentesis was additionally performed for every patient enrolled to obtain SAAG and other fluid parameters including complete blood count. On the other hand, 326 patients with acute Brucellosis without ascites were selected as a comparative group. All patients were treated with doxycycline plus rifampicin with respect to WHO guidelines. Patient consents were obtained.

Statistical Analysis

Descriptive statistics for continuous variables from the features mentioned; the average is expressed as standard deviation, minimum and maximum values, while categorical variables are expressed as numbers and percentages. One-way analysis of variance was performed to compare group averages for continuous variables. In determining the relationship between these variables, Pearson correlation coefficients were calculated separately in the groups. In determining the relationship between groups and categorical variables, Chi-square test was performed. The statistical significance level was taken as $p<0.05$ and the SPSS statistical software version 19.0 (SPSS Inc, Chicago, III, USA) pack has used for analyses.

RESULTS

Data of 20 patients with Brucellosis related ascites (with a male–female ratio of 1.5:1) were analyzed. In patients with ascites, the mean age was 43.6 ± 18.5 years. The mean age of control group without ascites was 56.7 ± 13.3. There was no significant difference between groups in terms of age and gender ($p>0.05$).

Serum acid albumin gradient was below 1.1 in all patients with ascites (0.6±0.3). The mean blood hemoglobin and hematocrit levels among ascites group were significantly lower compared to non-ascites group (11.1 ± 2.03 versus 12.12 ± 49.2; p=0.02; 33.56 ± 6 versus 37.350 ± 6,75; p=0.01 respectively).

The mean AST and ALT levels were found to be significantly higher in the ascites group compared to non-ascites group (630 ± 1405 versus 75 ± 336 and 454 ± 878 versus 51 ± 145 U/L.; all $p<0.001$).

Serum cholestatic enzyme levels were also analyzed as a categorical variable. Patients with ascites had a significantly higher serum alkaline phosphatase and gamma-glutamyl transferase levels compared to those without ascites (507 ± 489 versus 75 ± 336 and 183 ± 227 U/L, versus 70 ± 104 U/L.; all $p<0.001$).

In order to examine the role of Brucellosis-related pancreatitis on low gradient ascites, we also analyzed pancreatic enzyme profiles at both groups. Patients with ascites had higher levels both of amylase and lipase levels than those without ascites (1793 ± 2614 versus 75 ± 27 U/L; 1468 ± 1573 versus 57 ± 81U/L; all $p<0.001$). Additional analyses revealed that mean serum lactate dehydrogenase level was higher in ascites group (720 ± 469 versus 305 ± 108 U/L; p=0.03). In the acid fluid analysis of all patients, LDH level was found above 225 U/L (exudative).

The mean axial splenic vein diameters at both groups were measured using Doppler ultrasonography in combination with abdominal tomography. Statistical important difference was not found (134 ± 39 cm versus 122 ± 10 mm; p=0.318) (Table 2).

Inter-group comparisons were not significant for individual outcomes. No Brucellosis-related deaths were reported among study patients.

Table 1: Brucella species and Human prevalence (World Organisation for Animal Health 2006; Brucellosis in humans and animals)

Type	Reservoir	Other hosts	Prevalance in humans (%)
Brucellae mellitensis	Sheep, Goat, Camel	Cattle	70
Brucellae abortus	Cattle, Mandate, Jackal	Horse	25
Brucellae suis	Pig, Wolf, Fox	Cattle	5
Brucellae ovis	Sheep	-	No
Brucellae canis	Dog	-	Rare

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Table 2: Comparison of with acid and without acid patient parameters (AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDH: Lactate Dehydrogenase)

			n	Mean±Std. Dev.	Min-Max	P value
The mean of Brucella Aglutination Titer	Ascites	negative	326	541,29±447,752	160-1280	0,283
		positive	20	448,00±436,924	160-1280	
Age (years)	Ascites	negative	326	32,90±20,768	17-99	0,04
		positive	20	43,67±18,500	6-75	
Hemoglobin (gr/dl.)	Ascites	negative	326	12,125±2,0918	9,1-13,9	0,002
		positive	20	11,113±2,0336	7,7-13,6	
Hematocrit	Ascites	negative	326	37,350±6,7555	27,6-42	0,001
		positive	20	33,560±6,0085	22,8-42,1	
Platelet (/mm3)	Ascites	negative	326	259990±118617	21000-925000	0,549
		positive	20	235070±217370	33000-925000	
White Blood Cells (/mm3)	Ascites	negative	326	7,433±3,1274	1,7-25,8	0,879
		positive	20	7,080±3,3876	2,8-11,7	
ALT (U/L.)	Ascites	negative	326	51,4±145	5-2121	0,001
		positive	20	454±878	15-3044	
AST (U/L.)	Ascites	negative	326	75±336	9-5254	0,001
		positive	20	630±1405	13-5480	
Alkalyne phosphatese (U/L)	Ascites	negative	326	277±256	180-1838	0,001
		positive	20	507±489	83-1408	
Gamma glutamyl Transferase (U/L)	Ascites	negative	326	70±104.2	13-638	0,002
		positive	20	183±227	10,8-778	
Amylase (U/L)	Ascites	negative	326	75±27	13-174	0,001
		positive	20	1793±2614	55-8589	
Lipase (U/L)	Ascites	negative	326	57±81	5-536	0,00
		positive	20	1468±1573	21-4300	
Glucose(U/L)	Ascites	negative	326	97,37±31,759	56-366	0,08
		positive	20	153,83±58,854	56-254	
LDH (U/L)	Ascites	negative	326	305±108	178-411	0,002
		positive	20	720±469	327-1577	
Axial splenic diameter (mm)	Ascites	negative	326	122±10,001	100-220	0,318
		positive	20	134,42±39,330	98-220	

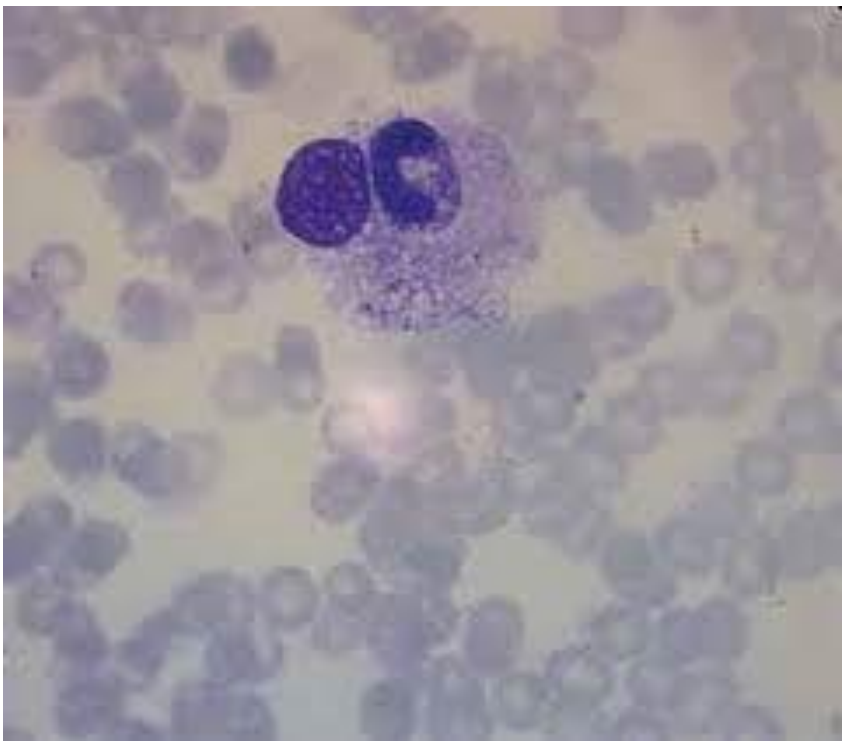

Figure: The presence of hemophagocytes in the bone marrow in a patient with Brucellosis (27).

DISCUSSION

Brucellosis is a worldwide zoonotic infection which caused by small, gram negative, oxidase and urease-positive coccobacilli from the genus Brucella, and mostly seen in Mediterranean Basin where the consumption of infected, unpasteurized animal-milk products (10). Although the Brucellosis is widely seen, it is mostly pandemic in the Mediterranean Basin, rural India and Central & South America (11). Due to extensive consumption of traditionally produced unpasteurized milk-based Turkish traditional cheese, human Brucellosis is also an endemic disease in rural areas of Turkey, where the annual incidence is 23 per 100.000 population (12).

The characteristics of ascites due to brucella have not yet been well established. According to limited case reports, patients with acute Brucellosis can develop pancreatic involvement or peritonitis, either of which could lead to ascites. Furthermore, presented cases with ascites, with a predominantly lymphocytic cell count, and may treated successfully with combination of tetracycline and rifampicin (3).

On the other hand, a case report revealed that acute Brucellosis might also cause portal hypertensive type ascites. Although the exact cause of this phenomenon was not clarified, this unique complication has been related to liver involvement of acute brucellosis infection by the authors (6).

Some authors hypothesize that the formation of ascites could be due to the primary reaction of the mononuclear–phagocytic system in the peritoneum to the infection, or to the underlying liver disease which is favored by Brucella infection (3). Our results strongly suggest that during acute phase of Brucellosis, inflammation of pancreatic tissue has a central role for developing exudative ascites via stimulating peritoneal inflammation. In the current study, the rate of Brucellosis-related ascites was 5.7%, which was higher than expected. This phenomenon might be due to more severe diseases in our patients.

Human Brucellosis may also cause spontaneous bacterial peritonitis in patients with liver cirrhosis. In the literature, there were few case reports regarding Brucellosis related peritonitis in patients with liver cirrhosis (13-17). There were also a few case reports regarding acute Brucellosis-related peritonitis in patients under peritoneal dialysis (7, 18, 19). But we did not detect spontaneous bacterial peritonitis in our cases. In those case reports; the exact cause of human Brucellosis involving cirrhotic patients mostly attributed to injured liver tissue resulting in increasing infectious mechanisms, in part through diminished opsonization and reduced anti-inflammatory signaling pathways. Those presented case reports were mostly originated from Turkey and successfully treated with six-weeks course of doxycycline plus rifampicin or doxycycline plus streptomycin regiments according to recommendations of the World Health Organization.

Lastly, two case reports involving Brucellosis-related pancreatitis were also described in patients with a ventriculoperitoneal shunt (20, 21). Brucellosis shows the involvement of thyroid gland involvement is rare (22).

In a large prospective study involving 158 patients with end-stage renal disease with Brucellosis revealed that percentage of Brucellosis-related peritonitis was as low as 0.6% (23).

In the current study we excluded patients who underwent ambulatory peritoneal dialysis. Described patients in those case reports were mostly immunocompromised patients and Brucellosis-related ascites might be related to lack of immunity against bacterial infections. Moreover, it has been shown that ascites are often present either as a temporary flare of underlying hepatic disease or as bacterial peritonitis during acute phase of Brucellosis (3). In the current study, we concluded that peritoneal and pancreatic involvement of Brucella infection causes exudative leakage from capillaries. In the current study, there was a relationship between the presence of ascites and elevated levels of cholestatic enzymes though which the mechanism was unclear. We postulated that this association might be due to presence of ascites, which was a strong finding of severe acute Brucellosis. On the liver perspective, data involving 100 patients with diagnosis of Brucellosis followed for at least one year from University Hospital of Ioannina revealed that mild hypertransaminasemia was seen in 24% of patients (5). It has been shown that cholestasis and hepatic granulomas can be present in liver-biopsy specimens in cases of both B. Melitensis and B. Abortus (24). In the current study, we found that, hypertransaminasemia was independently associated with increased risk of ascites. In a recent publication, we reported that acute Brucella infection could lead to pancreatitis. In this study, we also found that hyperglycemia, anemia, hypertransaminasemia and high cholestatic enzymes might represent new approaches for assessing disease severity in patients with Brucellosis and acute pancreatitis (25). We also identified four additional cases of acute pancreatitis secondary to Brucellosis for the literature (26).

CONCLUSION

We conclude that acute Brucella infection can lead to a unique low serum acid albumin gradient ascites probably resulting from pancreatic leakage followed by peritoneal accumulation of serum proteins.

On the other hand there were several strengths of the study. First, the findings of this study demonstrate that Brucellosis-related ascites is in low gradient nature and pancreatic type. Second, to the best of our knowledge, this is the first retrospective study comparing the Brucellosis patients with and without ascites. Further studies are needed to determine a causal link between human Brucellosis and exudative ascites.

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