



## Atypical cholecystitis due to brucellosis

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### ABSTRACT

Brucellosis is a common zoonotic bacterial infection seen all over the world. It causes economic losses and major health concerns in many developing countries. Humans are infected primarily through raw milk and dairy products, and to a smaller extent by direct contact with infected animals. Due to its various systemic symptoms, brucellosis is included in the differential diagnosis of many diseases. Cholecystitis is a rare complication of brucellosis. *Brucella* species can settle in numerous organs and cause atypical clinical forms due to their capacity to cause bacteremia. Brucellosis, an endemic disease in our country, may present with a variety of clinical symptoms and consequences, making diagnosis and treatment difficult. The purpose of this study was to evaluate the literature on gallbladder involvement, which is an atypical involvement of brucellosis.

**Keywords:** Brucellosis, cholecystitis, gallbladder.

Acute cholecystitis is one of the most commonly diagnosed diseases; more than 90% of cases arise after bile stasis due to gallstones in the gallbladder. The most common bacterial agents known to cause acute cholecystitis are *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, *Enterobacter spp.*, *Citrobacter spp.*, *Pseudomonas spp.*, *Salmonella typhi*, *Salmonella paratyphi*, *Streptococcus spp.*, *Enterococcus faecalis*, *Clostridium spp.*, *Bacteroides spp.*, *Proteus spp.* Although uncommon, *E. coli* producing multiple-resistant extended spectrum beta-lactamase, methicillin-resistant *Staphylococcus aureus*, and *Acinetobacter baumannii* are found in hospital-acquired cholecystitis. Among viruses, hepatitis A virus, hepatitis B virus, Epstein-Barr virus, and cytomegalovirus, and among parasites, *Ascaris lumbricoides*, *Fasciola hepatica*, *Clonorchis sinensis*, *Opisthorchis spp.* are the microorganisms reported to cause cholecystitis.<sup>[1-4]</sup>

Brucellosis, also known as Malta fever or Mediterranean fever, is a zoonotic infectious disease that can cause significant economic losses and serious health problems in developing countries. Unpasteurized milk and dairy products are the primary sources of infection in humans, but direct contact with infected animals is also possible. It is considered endemic in the Mediterranean basin, the Arabian peninsula, the Indian subcontinent, and parts of Mexico, Central, and South America. The disease's incidence ranges from 0.01 to >200 per 100,000 people, especially in endemic areas. Türkiye is one of the endemic areas for this disease, with an estimated incidence of 23/100,000 people. *Brucella* subtypes include *Brucella abortus*, *Brucella melitensis*, *Brucella suis*, and *Brucella canis*. *Brucella melitensis* is the most frequent in our country. Due to its many systemic symptoms, brucellosis is included in the differential diagnosis of many diseases. The most common involvement in brucellosis is osteoarticular involvement.<sup>[5,6]</sup> *Brucella spp.*, however, can settle in various organs and cause atypical clinical manifestations due to their potential to cause bacteremia. Cholecystitis is one of these rare involvements.<sup>[5,7,8]</sup> In this study, we aimed to evaluate gallbladder involvement, an atypical involvement of brucellosis that is endemic in our country, in the light of the literature.

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## BRUCELLA-INDUCED CHOLECYSTITIS

### General information

According to research, about 30% of patients with brucellosis experience gastrointestinal symptoms. The most prevalent gastrointestinal complication is reactive hepatitis with or without granulomas. Less common complications include appendicitis, peritonitis, intra-abdominal abscesses, colitis, ileitis, and pancreatitis. Acute cholecystitis as a brucellosis complication is relatively uncommon. *Brucella species* typically induce bacteremia and systemic infection. They can enter the gallbladder or liver via the blood or lymphatic system. There is insufficient data on the chronic carriage of these bacteria in the gallbladder, however, the microorganism can remain latent in the body for many years before causing symptoms.<sup>[5-7]</sup>

### Diagnosis

Physical examination is crucial in the diagnosis of *Brucella*-induced cholecystitis. Undulant fever may be observed in situations of fever. There may be a fever one week and fever-free the next. In conditions of cholecystitis, Murphy's sign may be positive on abdominal examination.<sup>[8]</sup>

If there is bone marrow involvement in laboratory tests, leukopenia, thrombocytopenia, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and C-reactive protein levels may increase.<sup>[5-7]</sup>

Imaging techniques include abdominal ultrasonography, whole-abdomen imaging, and magnetic resonance cholangiography. Gallbladder inflammation and wall thickness may occur in the absence of surrounding fluid or distension.<sup>[8]</sup>

There are two approaches for diagnosing brucellosis: direct diagnosis and indirect diagnosis. Isolation of the causative agent from blood culture, bone marrow, tissues, or other body fluids allows for direct diagnosis. In 15-70% of cases, blood culture positivity is identified. Culture positivity is most commonly detected on days 7-21. This period can be completed in three days using automated culture systems. The causative agent cannot be identified in

indirect diagnosis, and antibodies against the causative agent are examined. Serologic tests are more routinely employed in diagnosis since cultures give late results and the probability of growth in culture is low. The Rose Bengal test is a slide agglutination test that employs the *Brucella abortus* 99-S strain. The test is very sensitive (>99%), has low specificity, and has a high negative predictive value. The Wright test is a tube agglutination test. It is the most often utilized diagnostic test. In active infection, the titer is usually 1/160 or higher. In endemic locations, treatment might begin in the presence of 1/80 and symptoms.<sup>[7-12]</sup>

Granulomas may be found during a liver biopsy as part of the diagnostic.<sup>[6,7]</sup> In one case reported in the literature, *Brucella*-induced cholecystitis was diagnosed in a patient who had no growth in blood culture due to *Brucella melitensis* growth in gallbladder culture after postoperative cholecystectomy.<sup>[9]</sup>

### Treatment

Antibiotics that can affect the intracellular acidic environment and macrophages are employed in treatment. Due to the high relapse rates associated with monotherapies, combination treatments should be considered. Traditionally, medications such as trimethoprim/sulfamethoxazole, gentamicin, rifampicin, doxycycline, ciprofloxacin, and streptomycin have been used. The most common treatment regimens are doxycycline (six weeks) and streptomycin (two or three weeks) or doxycycline (six weeks) and rifampicin (six weeks). It is thought that the combination of doxycycline and streptomycin is more effective than the combination of doxycycline and rifampicin. Fluoroquinolones can also be used with doxycycline or rifampicin. The combination of doxycycline and streptomycin is commonly used in the presence of bone infections due to brucellosis and in cases of drug toxicity or relapse.<sup>[5,10]</sup>

In *Brucella*-induced cholecystitis, surgical treatment is unnecessary unless there is perforation of the gallbladder. In a case report, even in the presence of gallbladder empyema, medical treatment without cholecystectomy was reported to be successful.<sup>[8]</sup> Yet, even if a cholecystectomy is performed, it has been

**Table 1.** Cases of *Brucella*-induced cholecystitis reported since 2000

Autor	Year/Country	Age/Sex	Treatment
Al-Otaibi <sup>[6]</sup>	2010/Saudi Arabia	45/M	Medical
Miranda et al. <sup>[9]</sup>	2001/Spain	34/M	Surgical/Medical
Speiser et al. <sup>[14]</sup>	2019/United States	57/M	Surgical/Medical
Kanafani et al. <sup>[11]</sup>	2005/Lebanon	55/M	Surgical/Medical
Yildirim et al. <sup>[4]</sup>	2018/Türkiye	54/M	Medical
Ahbab ve ark. <sup>[16]</sup>	2015/Türkiye	57/M	Medical
Çeviker et al. <sup>[5]</sup>	2019/Türkiye	30/M	Medical
Hakyemez et al. <sup>[12]</sup>	2011/Türkiye	64/M	Medical
Köse et al. <sup>[8]</sup>	2017/Türkiye	69/F	Medical
Ergün <sup>[15]</sup>	2019/Türkiye	61/M	Medical
Ashley et al. <sup>[17]</sup>	2000/United States	6/M	Medical
Kanafani et al. <sup>[11]</sup>	2005/Lebanon	29/F	Medical
Androipoulos et al. <sup>[18]</sup>	2003/Greece	72/M	Medical
Lopez-Prieto et al. <sup>[19]</sup>	2003/Spain	56/F	Medical

reported that *Brucella*-induced cholecystitis cannot be treated without medical treatment.<sup>[11]</sup>

## REVIEW OF THE LITERATURE

Following the publication of the first case of *Brucella*-induced cholecystitis in 1934, similar cases were reported in the literature.<sup>[4]</sup> Morris et al.<sup>[13]</sup> published the first case in the PubMed database in 1979. While there was an increase in case reports worldwide between 1999 and 2010, the most current case was reported in 2019 by Speiser et al.<sup>[14]</sup>

Since 2000, the majority of the 14 cases (78.5%) reached were male. Most of the patients (72%) were over the age of 45. The youngest case was a Mexican-born child living in the United States. According to reports, the majority of cases responded to medical treatment, 21.5% were diagnosed postoperatively, and the vast majority (88%) were detected in endemic countries.<sup>[5-14]</sup> Table 1 shows cases reported in the literature since 2000.

In conclusion, acute cholecystitis caused by *Brucella* does not require surgical treatment. This may lead to reduced invasive interventions, lower mortality and morbidity, and, indirectly, lower healthcare costs. Brucellosis should

be considered in the differential diagnosis of cholecystitis, especially in endemic regions such as our country.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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