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Assessment of Brucellosis Seropositivity in Patients Diagnosed with Tularemia

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ABSTRACT

Objective: Tularemia and brucellosis share similar clinical manifestations and pathological characteristics. This study aimed to evaluate the demographic, clinical, and laboratory findings of patients diagnosed during a tularemia outbreak in whom brucellosis co-infection was suspected, to highlight the potential coexistence of these two zoonotic infections and contribute to effective disease management.

Materials and Methods: Following the tularemia outbreak in Sivas Province during the first half of 2024, the electronic medical records of Sivas Numune Hospital and Sivas Cumhuriyet University Hospital were retrospectively reviewed. Tularemia diagnosis was confirmed in patients presenting with compatible clinical features and a microagglutination test (MAT) titer of ≥1:160. Serum samples that were seropositive for tularemia were further analyzed for *Brucella* antibodies using the serum agglutination test (SAT). Titers of ≥1:160 in patients without a prior history of brucellosis were considered positive.

Results: Among 162 tularemia patients tested for *Brucella*, Rose Bengal and Wright agglutination tests were positive in 17 (10.4%) and nine (5.5%) patients, respectively. Five were female and four were male. Five patients resided in rural areas, and six reported involvement in livestock farming or agriculture. Fever was present in six of nine patients, while sore throat and fatigue were reported in all. Tonsillopharyngitis was detected in six patients, and lymphadenopathy was observed in all nine. The duration of symptoms at presentation ranged from 7 to 60 days, and seven patients had received antibiotic treatment before diagnosis.

Conclusion: This study is the first to evaluate tularemia cases with concomitant *Brucella* seropositivity. The findings suggest that, in brucellosis-endemic regions, *Brucella* serology should be routinely performed in patients with suspected tularemia to ensure accurate diagnosis and appropriate management.

Keywords: *Brucella*, co-infection, cross-reaction, outbreak, Tularemia.

INTRODUCTION

Tularemia is a zoonotic infection caused by *Francisella tularensis*, a small, gram-negative, non-motile, intracellular bacterium that has also been identified as a potential biological threat agent.[1] Although small mammals such as rabbits, squirrels, and mice serve as the principal reservoirs, humans may acquire the infection through multiple pathways, including consumption of contaminated food or water, direct contact with infected animal secretions, bites from contaminated arthropods such as ticks or flies, or inhalation of aerosols containing the organism. To date, transmission between humans has not been documented.[2] Typical manifestations of tularemia include fever, malaise, chills, and headache, while the clinical presentation varies according to the route of transmission and the anatomical site affected.[3]

Brucellosis, in contrast, is an infection caused by small, gram-negative, facultative intracellular coccobacilli that do not possess capsules or spores.[4] Humans typically contract the disease through ingestion of unpasteurized milk or other dairy products. Although direct transmission between individuals is uncommon, instances of sexual, congenital, and breastfeeding-associated spread have been reported.[5,6] The early clinical manifestations are usually nonspecific, presenting with symptoms such as fever, headache, malaise, joint pain, weakness, loss of appetite, and fatigue.[7]

Tularemia and brucellosis are two zoonotic infections that share overlapping clinical features. To the best of our knowledge, no case series or literature review has examined demographic, clinical, and laboratory characteristics—including *Brucella* seropositivity—among patients with tularemia. In this study, we analyzed cases suspected of tularemia–brucellosis co-infection identified during a tularemia outbreak. Our objective was to draw attention to the potential coexistence of these two diseases with similar clinical presentations and to contribute to their effective management.

MATERIALS AND METHODS

Following a tularemia outbreak that occurred in a province of Türkiye during the first half of 2024, a retrospective study was conducted using the electronic databases of Sivas Numune Hospital and Sivas Cumhuriyet University Hospital. The research protocol received approval from Sivas Cumhuriyet University Ethics Committee for Non-Interventional Research (approval number: 2024/06-36, date: 27.06.2024). A total of nine adult participants (≥18 years) showing seropositivity for both tularemia and brucellosis during the nearly six-month outbreak period were enrolled in the study. Patients under 18 years of age, pregnant women, and individuals with a prior history of brucellosis were excluded.

KEY MESSAGES

- First-time Tularemia–Brucella seropositive patients were analyzed.
- A significant proportion of cases (5.5%) were also positive for Brucella serology.
- It was concluded that Brucella serology should be evaluated in patients with suspected tularemia in Brucella-endemic areas.

Tularemia was diagnosed when the microagglutination test (MAT) titer reached ≥1:160 in patients exhibiting clinical signs suggestive of the disease, or when a fourfold or higher rise in MAT titers between paired sera obtained at least two weeks apart was observed.[8]

All MAT testing procedures were conducted at the National Reference Laboratory under the General Directorate of Public Health in Ankara.

For the laboratory diagnosis of brucellosis, patient serum samples were examined using both the Rose Bengal plate agglutination method (Brucellapleyt) and conventional tube agglutination assays, including the Wright and Coombs techniques. The antigen employed for the plate test was the Sero-Lam Brucella Rose Bengal Plate Test reagent (Seromed, Türkiye), while the Wright tube test utilized the Sero-Tüp Brucella Tube Agglutination antigen (Seromed, Türkiye). To detect incomplete or blocking antibodies that may prevent visible agglutination in standard tube assays, a Coombs tube agglutination test was also performed using AGH MAESTRIA IGG+C3D (Diagast, France) anti-human globulin. The Rose Bengal results were recorded as either positive or negative depending on the appearance of visible agglutination. For the Wright and Coombs procedures, serial serum dilutions starting at 1/20 were tested. Titers of 1:160 or higher were regarded as indicative of brucellosis in individuals without a prior history of the disease.

Epidemiological, demographic, clinical, and laboratory data of the patients were retrieved from the hospital electronic database and recorded twice for each patient using Microsoft Office 365 Excel (Microsoft 365, USA; https://www.office.com/): once at admission and again on the 7th day after admission. Continuous variables were summarized as mean ± standard deviation (SD), and categorical variables were expressed as percentages (%) or absolute frequencies (n).

Statistical Analysis

As this was a descriptive study, no inferential statistical methods were applied.

Table 1. Demographic and clinical characteristics of patients and risk factors for possible transmission

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age	30	37	43	69	60	57	33	30	43
Gender	F	M	M	F	F	M	F	F	M
Chronic disease	No	No	DM	DM	No	DM	No	No	No
Rural living	No	Yes	Yes	Yes	Yes	No	No	No	Yes
Animal husbandry/farming	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Consuming pasteurized milk and dairy products	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Type of drinking water consumed	Tap water	Spring water	Tap and spring water	Tap water	Spring water	Spring water	Spring water	Tap water	Tap water
Fever	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Sore throat	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fatigue	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Muscle-joint pain	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Tonsillitis-pharyngitis	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Tularemia form	Orop.	Orop.	Orop.	Orop.	Orop.	Orop.	Orop.	Orop.	Orop.
Symptom duration	7 days	14 days	45 days	35 days	45 days	20 days	60 days	45 days	20 days
Lymphadenopathy	Neck bilateral cervical	Neck left cervical	Left sub.	Left sub.	Neck right lateral	Left sub.	Left cervical	Right cervical	Right cervical
LAP size	27x16 mm	30x20 mm	45x18 mm	20x20 mm	60x30 mm	30x25 mm	60x50 mm	40x20 mm	40x20 mm

F: Female; M: Male; DM: Diabetes mellitus; Orop: Oropharyngeal; Sub: Submandibular; LAP: Lymphadenopathy.

RESULTS

A total of 162 patients diagnosed with tularemia were tested for *Brucella*, of whom 17 (10.4%) were positive by the Rose Bengal test and nine (5.5%) showed a significant titer in the Wright agglutination test. The ages of these nine patients ranged from 30 to 69 years; five were female and four were male. Five patients resided in rural areas, and six reported a history of livestock farming or agricultural work. Three patients who did not live in rural regions and were not engaged in animal husbandry reported consuming raw milk or dairy products. Fever was present in six patients, whereas sore throat and fatigue were reported in all nine. Tonsillopharyngitis was detected in six patients, lymphadenopathy in all, and unilateral lymphadenopathy in eight. The duration of symptoms before diagnosis ranged from 7 to 60 days, and seven patients had received beta-lactam antibiotics prior to diagnosis. Histopathological examination was performed in two patients, and both were reported as consistent with granulomatous lymphadenitis. Five patients were evaluated using mycobacteriological methods (acid-fast staining and/or culture), and all results were negative.

Demographic and clinical characteristics of the patients and possible transmission-related risk factors are presented in Table 1, laboratory findings in Appendix 1, and antibiotics used and post-treatment findings in Appendix 2.

DISCUSSION

Tularemia presents with a wide range of clinical manifestations in humans, including ulceroglandular, glandular, oculoglandular, pneumonic, typhoidal, and oropharyngeal forms.[9] In Türkiye, the oropharyngeal form is the most frequently observed. In this form, the bacteria enter through the skin or mucous membranes and spread to the lymph nodes, leading to necrotic inflammation and suppuration. Because tularemic lymphadenitis induces granulomatous inflammation, it may be misdiagnosed as other granulomatous diseases, particularly tuberculosis.[10] Furthermore, the causative agent possesses antigenic structures similar to those of the genera *Brucella* and Yersinia, which may result in serological cross-reactions.

In a study investigating the frequency of tularemia antibodies in patients with tuberculous lymphadenitis, 79 individuals were found to be seropositive for tularemia, and agglutination against *Brucella* spp. at significant titers (≥1:160) was detected in two of them.[11] In our study, 17 of 162 tularemia patients (10.4%) were positive by the *Brucella* Rose Bengal test, and nine (5.5%) showed significant titers in the Wright agglutination test. However, because tularemia and brucellosis present with overlapping clinical features, it was not possible to determine whether the symptoms observed were attributable to brucellosis; therefore, differentiation between acute and chronic infection could not be established.

Living in rural areas and engaging in agricultural or livestock activities are important risk factors for both tularemia and brucellosis.[12,13] Studies from different regions of Türkiye have reported that the prevalence of brucellosis in rural populations ranges between 3.4% and 8.5%, with significantly higher rates among individuals directly involved in animal husbandry.[14,15] In the study by Alim et al.,[15] 77.8% of brucellosis patients reported direct contact with animals, highlighting the importance of occupational exposure. In our study, five of the nine *Brucella*-seropositive tularemia patients lived in rural areas, and six had a history of livestock farming. Regarding tularemia, the primary route of transmission is the consumption of unchlorinated tap water or natural water sources such as springs, lakes, or streams,[13] and all patients in our study reported such high-risk water consumption. Due to the small sample size, these findings were evaluated only descriptively. Nevertheless, the results suggest that rural living conditions and contact with livestock may be more strongly associated with *Brucella* seropositivity among tularemia cases. These observations may serve as valuable guidance for future large-scale studies conducted in regions with similar epidemiological characteristics.

Both brucellosis and tularemia share nonspecific clinical features such as fever, fatigue, headache, and myalgia, which often complicate the differential diagnosis between the two diseases.[16,17] Lymphadenopathy, although a common finding, is not distinctive for either condition;[17] in our cohort, all patients presented with lymphadenopathy. Consistent with previous research indicating that the oropharyngeal form is predominant in Türkiye,[18–20] all nine cases in our study were classified as oropharyngeal tularemia.

The overlapping symptomatology of brucellosis and tularemia may also contribute to diagnostic delays and inappropriate treatment choices, particularly in regions where both infections are endemic. In non-endemic areas, a lack of clinical suspicion frequently results in missed or delayed tularemia diagnoses. Consequently, patients are often treated empirically with antibiotics ineffective against *Francisella tularensis*, most commonly beta-lactams.[18,19] Similarly, in our study, seven patients (77.7%) had received unnecessary beta-lactam antibiotics before the correct diagnosis was established. This finding highlights the ongoing challenge of distinguishing these two clinically similar infections and underscores the importance of heightened clinical awareness and early diagnostic testing in endemic regions.

While culturing *Francisella tularensis* is regarded as the definitive criterion for confirming tularemia, this procedure can only be carried out in biosafety level 3 laboratories. Consequently, molecular and serological diagnostic approaches are more frequently utilized in practice. Among serological techniques, the microagglutination test is considered the principal assay for confirming tularemia.[2] In a similar manner, isolation of *Brucella* species remains the reference method for verifying brucellosis in the laboratory; however, serological assays continue to be the most practical diagnostic alternatives. Among them, the standard agglutination test (SAT) is the most widely implemented, and titers of 1:160 or higher in individuals showing compatible clinical manifestations are interpreted as diagnostic for brucellosis.[21]

In our study, MAT titers for tularemia ranged from 1/640 to 1/1280, whereas SAT titers for *Brucella* were 1/160 in three patients and ≥1/320 in six patients. Several studies have reported serological cross-reactivity between *F. tularensis* and *Brucella* species.[11,22–25] Behan et al.[25] examined serum samples from 128 tularemia and 34 brucellosis patients and found significant agglutination against *Brucella* in seven tularemia sera. The same study also demonstrated notable tularemia-reactive antibodies in one brucellosis patient. Sato et al.[26] similarly reported low-level (titers 10–80) cross-reactive antibodies to B. abortus in six of fifteen patients with *F. tularensis* MAT titers exceeding 2,560. Maurin[27] further emphasized that, although sera from individuals harboring cross-reactive organisms may react with *F. tularensis* antigens, specific anti-*F. tularensis* antibodies are generally absent. He concluded that such immunological cross-reactions are limited in extent and exert minimal influence on the routine serological diagnosis of tularemia. Taken together, these findings from previous studies highlight the potential for serological overlap between tularemia and brucellosis, which should be carefully interpreted in endemic settings to avoid diagnostic confusion.

The presence of sacroiliitis in one of our patients supports the diagnosis of symptomatic acute brucellosis. Considering the widespread use of serological tests for *Brucella* and the frequent identification of asymptomatic infections based solely on serology, it appears reasonable to interpret the findings in our patients as possible co-infection, particularly in light of the endemicity of chronic, often subclinical, brucellosis in the region.[28,29]

Among the recommended treatment regimens for tularemia, aminoglycosides remain the first-line agents, while quinolones and tetracyclines are also considered effective alternatives.[18,30] Meric et al.[31] reported that doxycycline was associated with higher rates of treatment failure and recurrence compared with aminoglycosides and ciprofloxacin, and noted that suppuration occurred more frequently in patients receiving doxycycline. In our study, six patients were treated with doxycycline and rifampicin, whereas three received a combination of streptomycin and doxycycline. Only one patient developed lymph node suppuration, which occurred in the latter group. This patient had a symptom duration of 60 days at presentation, suggesting that the complication was likely related to delayed diagnosis and prolonged disease course. The duration of treatment was completed to six weeks in eight patients, and three underwent therapeutic lymph node excision or abscess drainage. No treatment-related adverse effects or recurrences were observed during the three-month follow-up period after completion of therapy. These findings support the use of aminoglycoside-based or combined regimens as effective options for managing tularemia cases, while emphasizing the importance of early diagnosis to prevent suppurative complications.

Given the limited number of patients included in this study (n=9), the generalizability of our findings is naturally constrained. Accordingly, these results should be regarded as preliminary and hypothesis-generating rather than definitive.

The principal limitation of this study lies in its retrospective design, which precluded the use of molecular diagnostic methods. Moreover, blood cultures were not performed to further substantiate the differential diagnosis of brucellosis. Consequently, it remains uncertain whether the observed epidemiological, clinical, laboratory, and pathological features truly represent tularemia–*Brucella* co-infection or merely reflect serological cross-reactivity between the two pathogens.

CONCLUSION

Nevertheless, the findings provide valuable insight into the diagnostic overlap between these two zoonotic infections and underscore the need for prospective, large-scale studies employing molecular confirmation to clarify this relationship.

In conclusion, tularemia and brucellosis share significant overlap in their epidemiological patterns, clinical presentations, and laboratory profiles, with both capable of inducing granulomatous inflammation in lymphatic tissues. Our findings highlight that, in regions where brucellosis is endemic, *Brucella* seropositivity may coexist with tularemia or mimic infection through serological cross-reactivity.

Given these diagnostic challenges, incorporating *Brucella* serology and obtaining blood cultures as part of the diagnostic work-up for suspected tularemia cases may improve diagnostic accuracy and help prevent potential misclassification. Furthermore, molecular confirmation methods should be employed in future studies to better differentiate true co-infection from serological cross-reactivity.

Although the small sample size limits the generalizability of our results, this study represents a preliminary but valuable contribution to understanding the clinical intersection between tularemia and brucellosis, providing a basis for larger, prospective investigations.

Ethics Committee Approval: Ethics committee approval was obtained from Sivas Cumhuriyet University Ethics Committee for Non-Interventional Research (date: 27.06.2024, number: 2024/06-36).

Informed Consent: Written informed consent was not required due to the retrospective nature of this study.

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Appendix 1. Laboratory results

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Total patients Mean (±SD)/ Median (IQR)
WBC (cells/mm³) (3,200–10,600 cells/L)										
Result at the time of admission	9570	7960	10270	11540	7550	9490	10600	5110	8000	8898 (±1949)
1st-week control test results	7100	10690	8770	8820	5070	8850	8630	5660	8800	8043 (±1771)
HGB g/dl (13.2–17.5 g/dl)										
Result at the time of admission	11	12	16	13.9	13.2	14	12.3	11.7	12.9	13 (±1.5)
1st-week control test results	12	13.2	15.9	14.3	12.9	15	12.6	11.9	12.5	13.3 (±1.3)
PLT (150–450)										
Result at the time of admission	292	291	294	337	217	328	399	232	236	291 (±58)
1st-week control test results	283	288	251	308	178	278	402	370	277	292 (±64)
ALT U/L (0–35 U/L)										
Result at the time of admission	120	25	38	16	5	15	10	18	20	17 (11–33)
1st-week control test results	33	32	34	19	2	12	12	20	15	19 (±11)
AST U/L (0–35 U/L)										
Result at the time of admission	65	22	25	19	16	19	15	28	17	19 (16–26)
1st-week control test results	17	27	17	24	14	21	15	29	19	20 (±5)
Sedimentation mm/h (0–20 mm/h)										
Result at the time of admission	96	53	10	32	25	21	41	45	43	40 (±24)
1st-week control test results	35	24	8	4	11	14	29	31	48	22 (±14)

Appendix 1 (cont). Laboratory results

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Total patients Mean (±SD)/ Median (IQR)
CRP mg/L (0–10 mg/L)										
Result at the time of admission	90	22	8.9	1.9	5	8	15	24	21	15 (6–23)
1st-week control test results	1.3	1.7	7.4	1.6	2	6	7	4	28	4 (1.6–7.2)
PCT ng/ml (0.5–2.0 ng/ml)										
Result at the time of admission	0.04	0.05	0.01	0.03	0.03	0.1	0.1	0.01	0.04	0.04 (±0.03)
1st-week control test results	0.02	0.02	0.03	0.02	0.01	0.1	0.05	0.6	0.2	0.05 (±0.06)
HBsAg	N	N	N	N	N	N	N	N	N	
Anti-HCV	N	N	N	N	N	N	N	N	N	
Anti-HIV	N	N	N	N	N	N	N	N	N	
Anti-HBs	N	N	N	N	N	N	N	N	N	
Anti-Toxo IgM	N	N	N	N	N	N	N	N	N	
EBV VCA IgM	N	N	N	N	N	N	N	N	N	
HSV IgM	N	N	N	N	N	N	N	N	N	
VDRL	N	N	N	N	N	N	N	N	N	
Brucella Rose Bengal	P	P	P	P	P	P	P	P	P	
Brucella Wright titer	1/640	1/320	1/320	1/1280	1/320	1/640	1/160	1/160	1/160	
MAT titer	1/640	1/1280	1/1280	1/640	1/640	1/1280	1/1280	1/1280	1/1280	
Acid-fast bacilli (AFB) staining	Not done	Not done	Not done	Not done	N	N	N	N	N	
Mycobacteria culture	Not done	Not done	Not done	Not done	No rep.	No rep.	No rep.	No rep.	No rep.	
Bacterial culture	Not done	Not done	Not done	Not done	No rep.	No rep.	No rep.	No rep.	No rep.	

WBC: White blood cell count; HBG: Hemoglobin; PLT: Platelet; ALT: Alanine Aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; PCT: Procalcitonin; HBsAg: Hepatitis B surface antigen; Anti-HCV: Antibody to hepatitis C virus; Anti-HIV: Antibodies to Human Immunodeficiency Virus; Anti-HBs: Hepatitis B surface antibody; Anti-Toxo IgM: Toxoplasma immunoglobulin M antibody; EBV VCA IgM: Epstein-Barr virus viral capsid antigen IgM; HSV IgM: Herpes Simplex Virus IgM; VDRL: Venereal Diseases Research Laboratory; MAT: Microagglutination Test; N: Negative; P: Positive; Rep: Reproduction; SD: Standard deviation; IQR: Interquartile range.

Appendix 2. Antibiotics and other methods used in treatment and post-treatment findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
History of antibiotic use before diagnosis	Amoxicillin-clavulanic acid	Ceftriaxone	Cefuroxime sodium	Ampicillin-sulbactam	Amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid	Amoxicillin-clavulanic acid	No	No
Antibiotic treatment after diagnosis	Doxycycline+ rifampicin	Streptomycin+ doxycycline	Doxycycline+ rifampicin	Doxycycline+ rifampicin	Streptomycin+ doxycycline	Doxycycline+ rifampicin	Streptomycin+ doxycycline	Doxycycline+ rifampicin	Doxycycline+ rifampicin
Duration of antibiotic treatment	6 weeks	Streptomycin 14 days + Doxycycline 6 weeks	6 weeks	6 weeks	Streptomycin 14 days + Doxycycline 6 weeks	6 weeks	Streptomycin 14 days + Doxycycline 6 weeks	12 weeks	6 weeks
Lymph node drainage/excision	Not done	Not done	Not done	Not done	Done	Not done	Not done	Done	Done
Response to treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
LAP status after treatment	Not detected	10x10 mm	10x10 mm	Not detected	10x20 mm	Not detected	10x10 mm	Not detected	Not detected
Relapse	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen	Not seen

LAP: Lymphadenopathy.