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Brucellosis in the Head and Neck: A Forgotten Differential Diagnosis

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Abstract

Introduction: Patients with brucellosis present with nonspecific symptoms originating from different organs. In this study, we aimed to investigate the symptoms related to the head and neck region in patients with brucellosis.

Materials and Methods: The retrospective study analyzed 542 patients with a definitive diagnosis of brucellosis who were admitted to our hospital between January 2015 and April 2022 and received outpatient and/or inpatient care. Clinical symptoms localized to the ear-nose-throat and head and neck regions were evaluated.

Results: A neck mass was detected in 52 out of 542 patients included in the study. The prevalence of cervical lymphadenopathy and/or abscess was 9.6%. Only lymphadenopathy was present in 30 (57.7%) patients, while both neck abscess and lymphadenopathy were detected in 22 (42.3%) patients. No significant difference was found between the two groups with regard to treatment regimens. Mean duration of treatment was 30 ± 22.1 (range, 14-70) days in the lymphadenopathy group and was 22 ± 14.7 (range, 14-60) days in the abscess group. No significant difference was found between the two groups with regard to the length of time to clinical recovery.

Conclusion: Brucellosis affects many regions of the head and neck and can have a variety of imaging manifestations that mimic benign and malignant lesions. The diagnosis of brucellosis should be considered in the first-line differential diagnosis conducted based on imaging features in patients residing in endemic regions.

Keywords: Brucella; head and neck, abscess; lymphadenopathy; granulomatous infection.

Introduction

The causative agent of brucellosis is Brucella spp., which is a gram-negative bacillus that can cause numerous diseases in both humans and animals and is reported to be the most common bacterial zoonosis worldwide. Approximately half a million brucellosis cases are reported annually worldwide and the reported prevalence is up to 10/100,000 in some countries (1). Brucellosis can be transmitted from animals to humans in numerous ways, predominantly through the consumption of unpasteurized raw milk and dairy products and less commonly via oral ingestion of infected meat or milk/milk products, contact with the tissues, damaged skin, or mucous membranes of infected animals, and inhalation of infected aerosols (2).The incubation period of brucellosis can vary between 7 days and 10 months and the peak incidence of the disease is in spring and summer, which are the breeding seasons of animals (3). Brucellosis is a systemic disease that can progress with a wide array of manifestations, ranging from asymptomatic to severe and fatal. Usually, acute or insidious symptoms appear within 2-4 weeks after infection. Complaints may be in the form of recurrent or chronic disease complaints, among which fever is the most common finding and may have a fluctuating course. Moreover, fever can be accompanied by various clinical conditions such as chills and shivering, sweating, fatigue, weakness, and muscle and joint pain. Bone and joints are the most common site of involvement in brucellosis (40%) and can present in the form of peripheral arthritis, sacroiliitis, spondylitis, osteomyelitis, and arthritis. Additionally, fatal conditions such as neurobrucellosis and brucella endocarditis can also be seen (2,4,5). Oral cavity is the primary site of contact with oral antigens and also the entry point for numerous orally ingested pathogens. Moreover, one of the main checkpoints for ingested microbial pathogens is the cervical lymph nodes, which is highly important in brucellosis (6). In this study, we aimed to investigate the symptoms localized to the head and neck system in patients with brucellosis who were diagnosed

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and treated at a tertiary hospital in a region where brucellosis is endemic.

Materials and Methods

The retrospective study analyzed 542 patients with a definitive diagnosis of brucellosis who were admitted to our hospital between January 2015 and April 2022 and received outpatient and/or inpatient care. Patient records were examined for medical history, clinical and laboratory findings, clinical outcomes, and complications. Brucellosis was diagnosed using Standard Tube Agglutination (STA) and Rose Bengal (RB) tests. The diagnosis was made in the presence of brucella bacteria growth in tissue culture, blood culture, or abscess growth but had clinical symptoms such as fever, fluid obtained from patients whose neck abscess was drained, or in patients who had no bacterial arthritis, and arthralgia (7). RB test was evaluated with STA test among the patients who applied with symptoms. Patients with positive Wright and/or Coombs Wright test (≥1/160 titer) were included in the study. Of the 542 patients, 52 patients were detected with lymph nodes and/or abscess in the neck and were included in the study (7). All the 52 patients were consulted to the ear-nose-throat (ENT) department. Demographic and epidemiological data, presenting symptoms, imaging methods, treatments, and prognoses were evaluated for each patient. Patients were divided into two groups: Group I; brucellosis + lymphadenopathy (Figure 1), and group II;

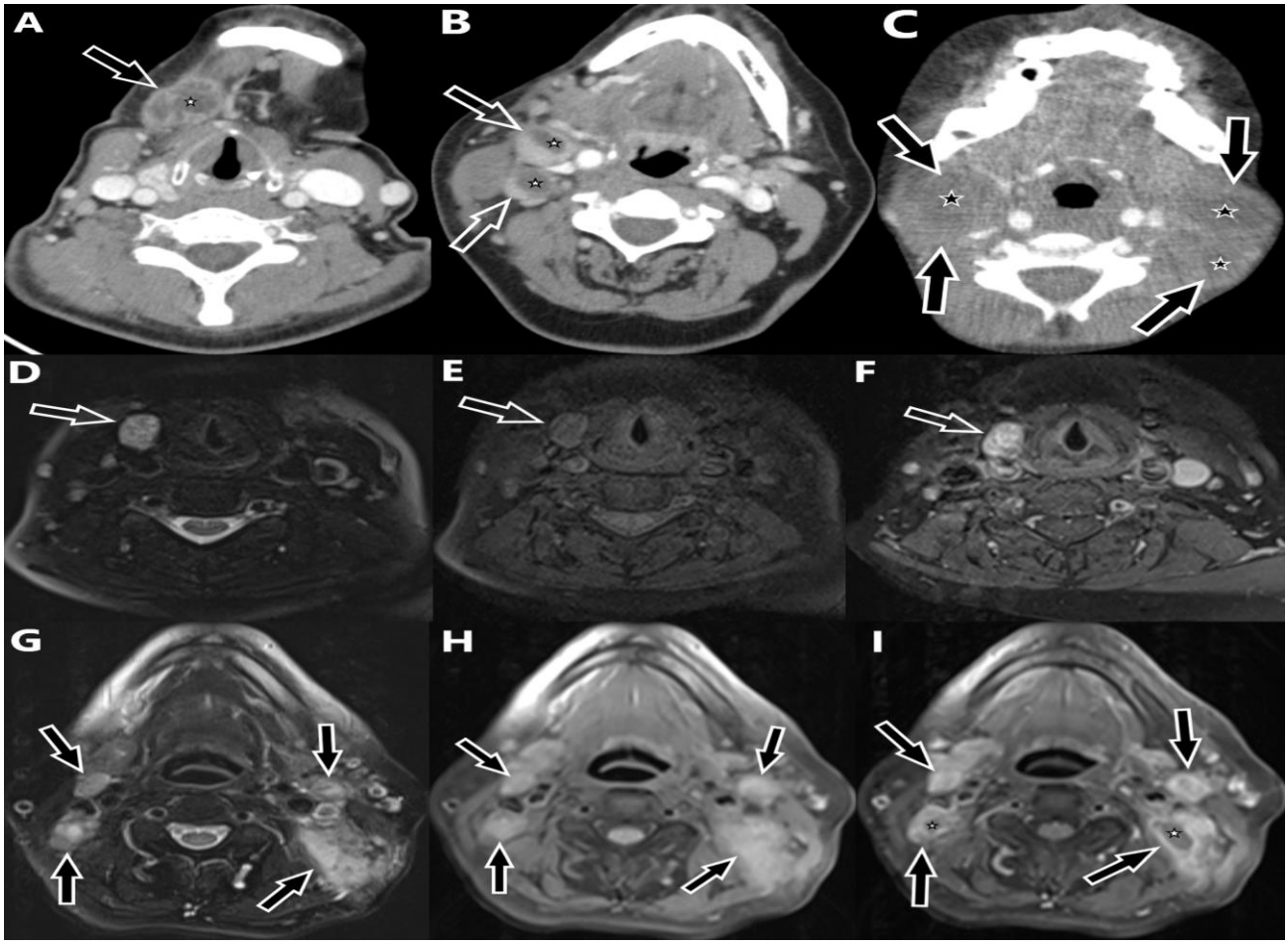

Figure 1: Lymphadenopathies (arrows) with central cystic-necrotic areas (stars) detected in contrast-enhanced axial neck CT sections; A. In a 57-year-old female patient, approximately 3x2.5 cm in size in the right submental region; **B.** In a 61-year-old female patient, approximately 2x1.5 cm in size in the right submandibular region; **C.** In a 16-year-old male patient, approximately 4x3cm in size in both jugular regions. In a 57-year-old female patient, lymphadenopathy with a size of 18x11 mm at level 4 in the right half of the neck in contrast-enhanced axial neck MRI sections; **D.** hyperintense on T2-weighted images; **E.** isointense on T1-weighted images; **F.** homogeneous contrast enhancement on contrast-enhanced T1-weighted images (arrows). In a 64-year-old female patient, 3x2 cm in size in both neck halves, the largest abscess localized to the left, in contrast-enhanced axial neck MRI sections; **G.** hyperintense on T2-weighted images; **H.** isohyperintense on T1-weighted images; I. lymphadenopathies (arrows) with heterogeneous contrast enhancement on contrast-enhanced T1-weighted images, with areas of central necrosis (stars) in large lesions.

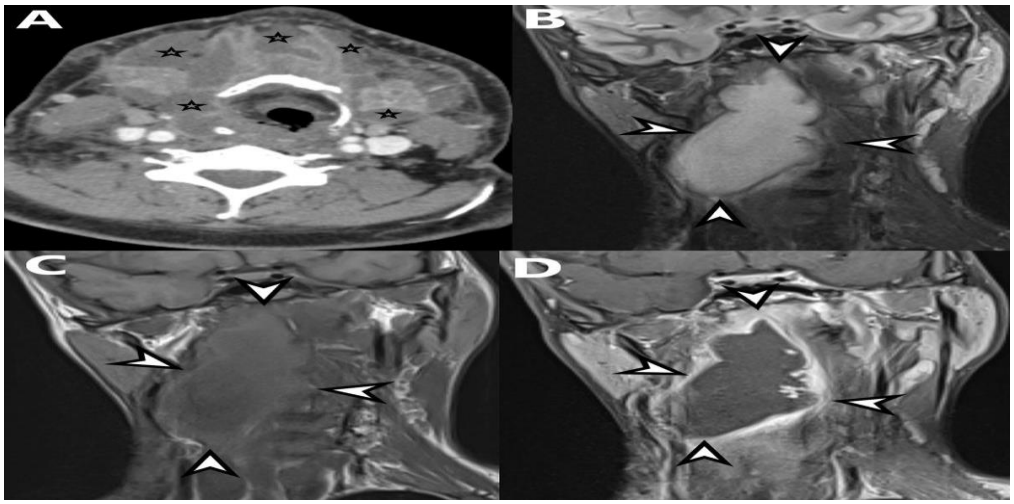

Figure 2: A. In a 64-year-old male patient, peripheral contrast-enhancing fluid loculations suggestive of diffuse abscess formations (stars) in both halves of the neck in contrast-enhanced axial neck CT sections. In a 22-year-old male patient, in the right half of the neck in in contrast-enhanced coronal neck CT sections; **B.** hyperintense on T2-weighted images; **C.** isointense on T1-weighted images; **D.** a 10x5 cm abscess formation (arrowheads) with peripheral contrast enhancement on contrast-enhanced T1-weighted images.

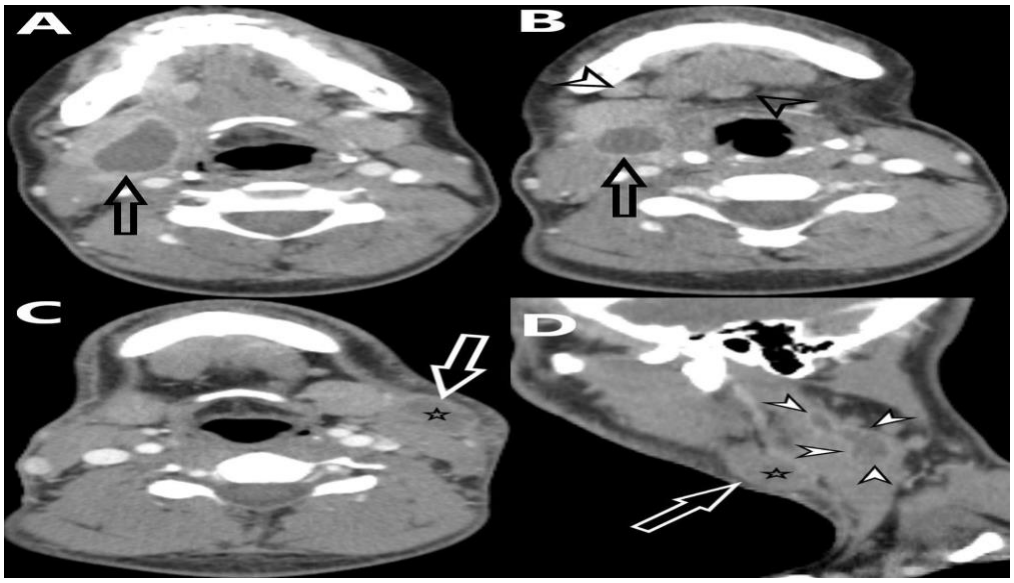

Figure 3: In a 28-year-old female patient, in contrast-enhanced axial neck CT sections; **A-B.** in the posteromedial aspect of right submandibular gland, an approximately 3x2 cm abscess suggestive of peripheral enhanced fluid loculation (arrows), **B.** lymphadenopathies smaller than 2 cm in the submental region (arrowheads). In a 35-year-old male patient, in contrast-enhanced neck CT sections; **C-D.** in axial-sagittal sections, 2x1.5 cm central necrotic (stars) lymphadenopathy (arrows) anteriorly adjacent to the sternocleidomastoid (SCM) muscle in the left submandibular region, **D.** in sagittal sections, a 4x1.5 cm peripheral contrast-enhanced fluid loculation suggestive of abscess formation (arrowheads) in the mid-section of the left SCM muscle in the posterior region.

brucellosis + abscess (Figure 2) ± lymphadenopathy (Figure 3) formation. In patients with neck involvement and an abscess larger than 2 cm, imaging-guided drainage was performed and antibiotic therapy was initiated. In patients with neck involvement and an abscess smaller than 2 cm, only antibiotherapy was initiated and drainage was administered depending on the clinical response. Radiological examinations were conducted using ultrasonography (USG). In patients without complications or clinical improvement, computed tomography (CT) and magnetic resonance imaging (MRI) were performed when necessary. Patients were treated using the antibiotic combinations recommended by the World Health Organization (WHO) (7), which included oral doxycycline (100 mg every 12 hours), oral rifampin (300 or 600 mg

every 24 hours), intramuscular streptomycin (1 g every 24 hours), oral amoxicillin clavulanic acid (1000 mg every 12 hours), oral ciprofloxacin (500 mg every 12 hours), co-trimoxazole (80/400 or 160/800 every 12 hours), or gentamicin (3-5 mg/kg/day). Ceftriaxone was added to the regimen for patients with neurobrucellosis. The duration of treatment was 6-12 weeks for patients with osteoarticular involvement, 12-24 weeks for patients with neurobrucellosis, and 6-12 weeks for patients with other clinical forms. Levamisole was added to the regimen for patients with chronic diseases (6 weeks, 80 mg every other day) and the duration of treatment was extended to 12-24 weeks. Baseline hearing test was performed before the treatment for patients initiated on aminoglycoside class antibiotics. Additionally, these patients were evaluated with pure-tone audiometry including high-frequency ranges, and hearing monitoring was performed on a weekly basis. All patients were followed up for at least 2-3 weeks throughout hospitalization. Outpatients were called for follow-up at 2-week intervals. At each follow-up visit, complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and liver enzymes were evaluated. All patients were followed up for at least one year after the treatment. Patients were recalled for the first follow-up visit two weeks later and then at 4, 8, and 12 weeks, 4 and 6 months, and 1 year. During the follow-up period, culture analysis and serological tests were performed only in patients suspected with recurrence.

Ethical approcal: The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the Clinical Researches Ethics Committee of Van Training and Research hospital (03/04.12.2021).

Statistical analysis: Data were analyzed using SPSS for Windows version 26.0 (Armonk, NY: IBM Corp.). Descriptives were expressed as mean ± standard deviation (SD) or median (minimum-maximum) and categorical variables were expressed as frequencies (n) and percentages (%). Independent Samples t-test was performed to compare groups. Statistically significant level was considered as %5.

Results

A neck mass was detected in 52 (9.6%) out of 542 patients included in the study. The patients comprised 30 (57.7%) men and 22 (42.3 %) women with a mean age of 33.3 ±17.2 (range, 5-62) years. Most common systemic symptoms included fever, arthritis, and night sweats (Table 1).

Table 1: Clinical characteristics of patients with brucellosis

	n (%)
Fever	30 (58)
Osteoarticular pain (arthritis)	1 (2)
Fever + Osteoarticular pain (arthritis)	9 (17)
Fever + Osteoarticular pain (arthritis) + Night sweats	6 (12)
Fever + Osteoarticular pain (arthritis) + Weight loss	2 (4)
Fever + Spondyloarthritis	2 (4)
Fever + Intracranial abscess and meningitis	1 (2)
Fever + Breast abscess	1 (2)

Table 2: Clinical head and neck symptoms of patients with brucellosis

	Right	Left	Bilateral
Lymphadenopathy (Group I)			
<3 cm	3	6	4
3-6 cm	8	4	4
>6 cm	1	-	-
Lymphadenopathy with Neck abscess (Group II)			
<2 cm	6	5	5
>2 cm	-	4	-
Parotid abscess <2 cm	1	-	-
Thyroid Abscess >2 cm	-	1	-

Only lymphadenopathy was present in 30 (57.7%) patients (Figure 1), while both neck abscess with or without lymphadenopathy were detected in 22 (42.3%) patients (Figure 2, 3). Patients with neck abscess and lymphadenopathy were categorized into the abscess group (group II), (Table 2). Lymphadenopathies smaller than 2 cm seen on CT were iso- or hypo-dense compared to muscles and exhibited mild homogeneous contrast enhancement (Figure 3B). Fatty planes adjacent to lymph nodes were intact. Lymphadenopathies smaller than 2 cm seen on MRI showed high signal intensity compared to muscles on T2-weighted images (Figure 1D), low-to-moderate signal intensity on T1-weighted images (Figure 1E), and homogeneous contrast enhancement

(Figure 1F). In all lymphadenopathies larger than 2 cm, contrast-enhanced CT and MRI showed necrotic features with central fluid density and cystic components in intensity (Figure 1A-C, 1G-I, 3C-D). Abscess formations accompanying lymphadenopathy had an impression of fluid loculations with peripheral subtle enhancement on contrast-enhanced CT and MRI (Figure 2). The amoxicillin clavulanate + ciprofloxacin combination was the most commonly administered treatment combination, which was administered to 16 patients in group I and in 15 patients in group II (14-60 days). The doxycycline + rifampicin + streptomycin combination was the second most frequently administered combination and it was administered to 12 patients in group I and in five patients in group II (14-70 days). The gentamicin + rifampicin + trimethoprim sulfamethoxazole (co-trimoxazole) combination was administered to one patient in group I and in two patients in group II. No significant difference was found between the two groups with regard to treatment regimens (p=0.37). Mean duration of treatment was 30 ± 22.1 (range, 14-70) days in the lymphadenopathy group and was 22 ± 14.7 (range, 14-60) days in the abscess group. No significant difference was found between the two groups with regard to the length of time to clinical recovery (p=0.34). In hearing monitoring, no sensorineural hearing loss, tinnitus, or vertigo was detected in any of the 21 patients that received. In the remaining 490 patients without lymph nodes and/or abscess in the neck, 7 patients received gentamicin and 32 patients received streptomycin in combination to other antibiotic drugs. Moreover, mild sensorineural hearing loss developed in two patients who received systemic aminoglycoside therapy, and the treatment strategies of these patients were changed.

Discussion

Brucellosis is an important public health problem with a wide array of clinical manifestations particularly in endemic regions. Although the disease can be seen in almost all regions of the world, it is more prevalent in countries in the Mediterranean basin (2,3). In addition, it is more common in the young age group (20-40 years) in endemic countries (8,9) Similarly, in our study, mean age of the patients was 33.3 ±17.2 years. Brucellosis shows a wide clinical variety and may show focal involvement in any organ or tissue in the human body, with the main symptoms including high fever, muscle pain, and arthritis pain (10,11). Studies have shown that many pathogens, particularly viruses as well as protozoa and bacteria, enter the body through the oral mucosa and drain into cervical lymph nodes (12) It is commonly known that brucella species evade the host immune response by developing various strategies. It has also been shown that antigen-presenting cells induce both natural and acquired responses by affecting many cells such as natural killer (NK) cells, CD4+ and CD8+ T cells, and B cells, thereby causing lymphadenopathy and occasionally abscess formation (13). Buchanan et al. (14) reported that all of their patients with brucellosis had fatigue, chills, sweating and also noted that 95% of the patients had fever and the most physical findings were limited to lymphadenopathy (14%) and splenomegaly (10%). Another study reported that lymphadenopathy was the third most common symptom in human brucellosis, occurring in slightly more than 1/3 of the cases Von Bargen et al. (15) analyzed 307 brucellosis patients who were followed up to the age of 14 years and reported that cervical lymphadenopathy was detected in 36% of the children. In the animal experiment developed by the authors, most of the orally administered brucella bacteria were detected in cervical lymph nodes. Based on this finding, the authors concluded that cervical lymph nodes play a significant role in oral infections both as an initial and effective trap for bacterial invaders and also as a possible reservoir for chronic pathogens (6). In another study, the prevalence of cervical lymphadenopathy was reported as 9.1% (16). In our study, the prevalence of cervical lymphadenopathy and/or abscess was 9.6%, which could be due to the widespread consumption of cheese produced from raw milk in our region. Moreover, in all these patients, both cervical lymphadenopathy and abscess were accompanied by symptoms such as fever and/or arthritis. The most vulnerable areas of the body to brucellosis are the osteoarticular and genitourinary systems, in which abscess formation is the most common occurrence (9). Abscesses in the head and neck region are mostly of odontogenic origin in adults and of tonsillar origin in children (17). In the literature, cases of thyroid and neck abscesses due to brucellosis have been reported (18,19) Since most neck abscesses are considered surgical emergencies, there are no studies reporting on the most ideal procedure and antibiotic regimen or the most optimal duration of treatment. The only definitive data is that drainage and antibiotic treatment are recommended in almost all patients with a neck abscess (17) As a matter of fact,

abscess formation is not uncommon due to the potential of brucellosis to produce chronic granulomatous lymphadenopathy. Abscess formation in granulomatous diseases results from the inability of macrophages to kill ingested organisms. Additionally, inflammatory complications are a major contributor to morbidity in chronic granulomatous diseases and are often resistant to standard treatments (20). In our study, coexistence of a neck abscess with lymphadenopathy was detected in 22 (42.3%) patients and most of these abscesses were found to be in the form of necrotizing lymphadenitis. In addition, large-size abscesses were also seen in the neck (Figure 2). In the statistical analysis, however, no significant difference was found between the two groups with regard to treatment duration. Imaging methods are commonly preferred in the differential diagnosis of cervical lymph nodes although these methods do not provide a definitive diagnosis when compared to histopathology. In cervical necrotizing lymphadenitis, loss of normal coffee bean shape or central fatty hilum and necrosis are well-known imaging features that indicate chronic granulomatous diseases such as malignancy and tuberculosis (21,22). A recent study demonstrated that the CT findings had a high accuracy in differentiating malignant tumor metastasis, tuberculous lymphadenitis, and lymphoma (23). In our study, necrotizing lymphadenitis due to brucellosis showed higher signal intensity similar to that of metastasis and tuberculosis (Figure 1, 2, 3). Additionally, given that brucellosis is a chronic intracellular disease, the imaging findings were suggestive of centrally liquefied, multiseptate, transpatial cold abscess lesions. Accordingly, we suggest that necrotizing lymphadenitis due to brucellosis and accompanying abscess formations should be kept in mind in patients that present with an unknown etiology of swelling in the neck and high signal intensity and reside in some endemic regions, as in our study. Given that brucella spp. is an intracellular bacterium, antibiotic regimens with intracellular efficacy and synergism are essential in the treatment. The use of a single antibiotic may result in recurrence, and relapse may occur within six months after completion of the treatment, with the most common causes of relapse including early termination of treatment, incomplete antibiotic treatment, and the presence of a localized focus of infection. On the other hand, it is highly important to plan appropriate antibiotic combinations in the treatment of brucellosis (7) In the study reporting on Ioannina recommendations, the doxycycline-streptomycin and doxycycline-rifampicin regimens were suggested as first-line treatment regimens with no distinction between them. The same study also noted that alternative therapies and triple drug regimens including fluoroquinolones and some other antibiotics such as co-trimoxazole and their combinations with rifampicin are still under investigation (24) Aminoglycosides are inexpensive and easily accessible broad-spectrum antibiotics that are highly preferred in the treatment of brucellosis. However, they are less preferred by clinicians due to their potential side effects (25) The incidence of hearing loss induced by aminoglycosides varies between 1-33%, while the incidence of vestibular toxicity is approximately 15%. Moreover, their usage in developed countries is remarkably low due to its significant toxicity and the availability of better alternatives in the market (26). Risk factors for ototoxicity include patient age as well as the agent used for the treatment and its cumulative dose and technique/time of administration. Additionally, genetic predisposition is also considered to play an important role. On the other hand, given the potential adverse effects of these combinations, it is recommended to monitor the ototoxicity and nephrotoxicity of aminoglycoside-containing regimens (27) In our study, 60 (11%) out of 542 patients received aminoglycosides in their treatment regimens. Among these, only two patients developed mild sensorineural hearing loss and their treatment regimens were changed. Our study was limited since it was a retrospective and single-center study. Further studies are needed to substantiate our findings.

Study limitations: The limitation of the study is that it is retrospective.

Conclusion

Brucellosis affects many regions of the head and neck and can have a variety of imaging manifestations that mimic benign and malignant lesions. The diagnosis of brucellosis should be considered in the first-line differential diagnosis conducted based on imaging features in endemic regions. In addition, the differential diagnosis of brucellosis should be considered in patients presenting with infective/inflammatory lesions that do not respond to conventional antibiotics, anti-inflammatory therapy, or for mass lesions with unusual appearances that are biopsy-negative for malignancy. Moreover, early initiation of

treatment will prevent debilitating complications, morbidity, and mortality.

Ethical approval: The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the Clinical Researches Ethics Committee of Van Training and Research Hospital (03/04.12.2021).

Conflict of interest: The authors declare that this article sent for publication in your journal is original, the scientific and ethical responsibility belongs to us and there is no conflict of interests.

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Author contributions: YSÇ: Conception and design of the study, Acquisition of data, Conception and design of the study, Analysis and interpretation of data, Final approval of the version to be submitted; İD: Conception and design of the study, Acquisition of data, Drafting the article, Final approval of the version to be submitted;

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