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Original Article

Cervical lymphadenopathy in tularemia: the role of diffusion-weighted magnetic resonance imaging in differentiating lymphadenopathies due to metastatic tumors

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ABSTRACT

Aim: To evaluate the role of diffusion-weighted magnetic resonance imaging (DW-MRI) in differentiating enlarged cervical lymph nodes due to tularemia and metastatic tumors.

Methods: We evaluated 59 patients with cervical lymphadenopathy (LAP) (32 patients with tularemia, 27 patients with metastatic tumors), retrospectively. We analyzed contrast enhancement patterns of LAP in postcontrast fat sat T1WI. We evaluated T2, DWI, and ADC signals of LAP in a 5-point scale system. Moreover, the mean ADC values of solid and necrotic LAP in both groups were quantitatively measured and compared statistically. Receiver operating characteristic curves of quantitative ADC values were obtained to determine the diagnostic performance.

Results: There was no difference between solid and necrotic LAP enhancement patterns in two groups. Solid LAP and peripheral parts of necrotic LAP showed diffusion restriction, whereas central parts necrotic LAP had high ADC and low DWI signal in both tularemia and metastatic groups. Signal characteristics were similar in two groups. In solid LAP, there was no significant difference between ADC values in two groups. In necrotic LAP, total, central, and peripheral quantitative ADC measurements were higher in the metastatic group than in the tularemia group.

Conclusions: Conventional MRI findings were not sufficient to differentiate metastatic LAP from tularemia. DW-MRI was not helpful in solid LAP; however, ADC values of metastatic necrotic LAP were significantly higher than tularemia. Microagglutination tests would be useful for differentiation; however, DW-MRI might also be useful for differentiation and may expedite the diagnosis.

Keywords: Cervical LAP, tularemia, metastatic tumors, necrotic LAP, MRI, DW-MRI.

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Introduction

Tularaemia is a zoonotic bacterial infectious disease caused by a gram-negative coccobacillus, Francisella tularensis. It is a rare pathogen for the urban population; however, it is more common in rural areas and a potential agent for bioterrorism. Diagnosis of tularaemia is difficult due to; its rarity and inconsistency of clinical findings, fastidious nature that causes weak growth in standard culture media, and confusing histopathological appearance mimicking tuberculosis [1-4].

The disease is commonly found in the soft tissue of the head and neck region. Imaging is mainly used to show the lesion and its extension. Since tularaemia is usually presented as neck masses with confusing clinical findings, differentiating them from malign lymphadenopathies is essential. Therefore, in addition to conventional contrast-enhanced MRI, diffusion-weighted magnetic resonance imaging (DW-MRI) findings could be helpful for differential diagnosis. DW-MRI is a recognized and reliable tool to evaluate and characterize lymph nodes. It is based on diffusion properties of water protons in biologic tissues, including the diffusion of molecules in extracellular or intracellular spaces as well as in cell membranes. There were numerous reports of DW-MRI characterization of malign, and benign lymph nodes might be completed without the need for invasive procedures [5-8]. The aim of this study is to evaluate the DW-MRI features of lymph node involvement due to tularemia and metastatic tumors in the head and neck region and to show the similarities and differences between them.

Materials and Methods

We obtained medical records of the patients who had tularaemia diagnosis serologically in our institution between June 2009 and June 2019. All patients underwent neck ultrasonography (US) and neck magnetic resonance imaging (MRI). Ethics committee approval was obtained and informed consent was waived by ethics committee because of the retrospective study design. Informed consent was waived because of the retrospective design and institutional ethical board approved our study (Decision No: 2020/28 Date: 18.02.2020) Patients were divided into two main groups as tularemia and metastasis. Both groups were divided into two subgroups as solid and necrotic. Serological diagnosis of tularaemia was made with the existence of specific antibody titers of ≥1:160 or with at least a fourfold increase of antibody titer in two serum samples taken two weeks apart in patients with clinical findings and symptoms which is compatible for tularaemia [9]. Thirty-nine patients were meeting these criteria. We excluded seven patients because they had undergone biopsy or surgical drainage before the MRI examination.

Patients in the metastatic group, who had a histopathological diagnosis of metastasis and neck US and neck MRI in our hospital between June 2009 and June 2019, were obtained. Twenty-nine patients were meeting these criteria. We excluded two patients from the study. One of the patients had insufficient biopsy material and discontinuation of the follow-up. Other patient presented with caseified granulomatous lymphadenitis.

All patients underwent MRI examination with a 1.5 Tesla MRI machine (Symphony; Siemens Medical Systems, Erlangen, Germany). A head and neck surface coil was used. MR images of patients were uploaded to a workstation (syngoMMWP VE25A, Siemens AG, Berlin, and Munich, Germany) for evaluations and measurements. Neck US images were not in PACS; therefore, we used US reports for comparisons.

MRI technique

T1-weighted images (TR/TE of 800/20 ms) and T2-weighted fast spin-echo images (TR/TE of 6.100/85 ms) were obtained from all patients. For MR images, the section thickness was 5 mm, interslice gap was 1–2 mm, field of view (FOV) was 25–30 cm, and the acquisition matrix was 256x224. For diffusion-weighted magnetic resonance imaging (DW-MRI), a multislice, single-shot, spin-echo, echo-planar imaging sequence was used. The section

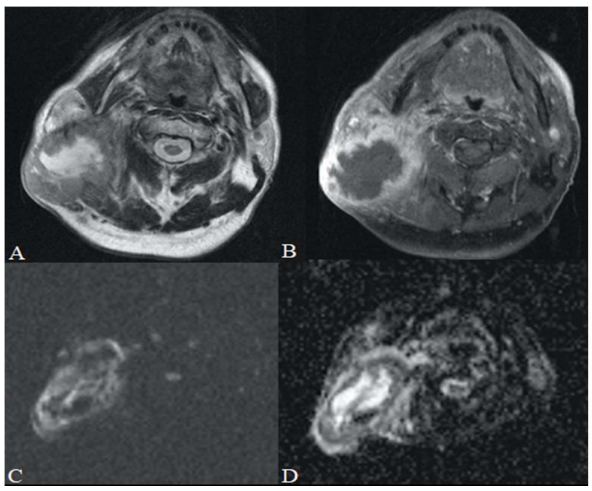

Figure 1. Metastatic necrotic LAP on the right side of the neck. **(A)** Central hyperintensity on Axial T2 weighted image. **(B)** LAP shows peripheral enhancement on T1 weighted image after contrast administration. **(C)** Axial DW-MRI of the necrotic LAP shows slight hypointensity on the central part and hyperintensity of the peripheral part of the lesion. **(D)** On the axial ADC image, necrotic LAP shows hyperintensity on the central part.

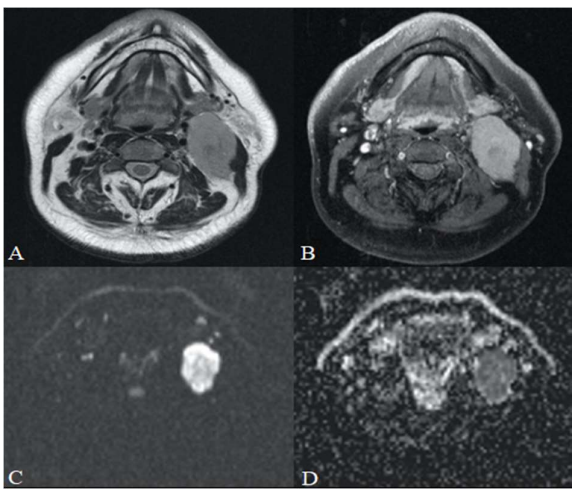

Figure 2. Metastatic solid LAP on the left side of the neck. **(A)** LAP shows intermediate signal on Axial T2 weighted image, **(B)** homogenous enhancement on T1 weighted image after contrast administration, and **(C and D)** restricted diffusion on DW-MRI.

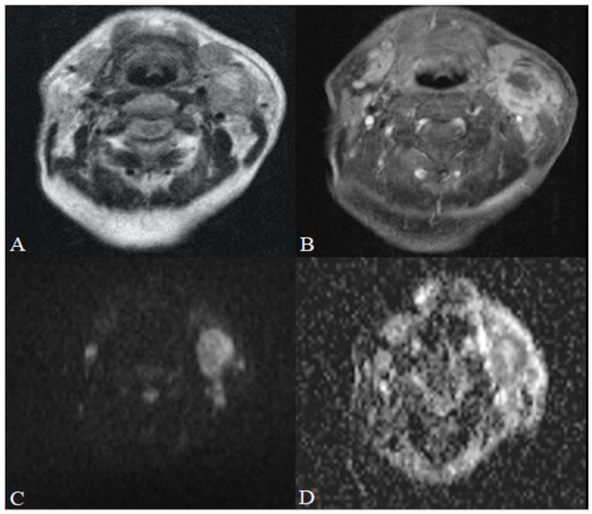

Figure 3. Necrotic LAP in tularemia on the left side of the neck. **(A)** Central hyperintensity on Axial T2 weighted image, **(B)** peripheral enhancement on postcontrast T1 weighted image. **(C)** Axial DWI of the necrotic LAP shows slight hypointensity on the central part of the lesion in comparison to hyperintensity of the peripheral part and **(D)** hyperintensity on the central part on axial ADC image.

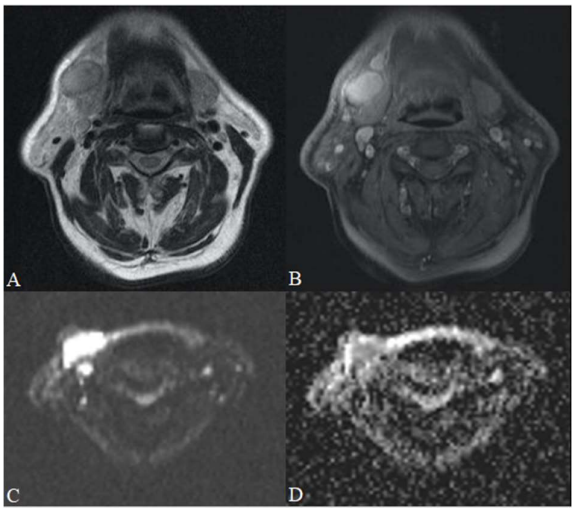

Figure 4. Solid LAP in tularemia on the right side of the neck. **(A)** LAP shows a slightly high signal on Axial T2 weighted image, **(B)** homogenous enhancement on T1 weighted image after contrast administration, and **(C and D)** restricted diffusion on DW-MRI.

thickness was 5 mm, TR:0.300 ms, TE: 70 ms, FOV read 400 mm, and FOV phase 66.7%. DW-MRI was obtained with a diffusion factor b of 0, 400, and 800 s/mm^2 with ADC maps in all patients.

Image interpretation

Images and information of a total of 59 patients, 32 in the tularaemia group and 27 in the metastasis group, were scanned from the hospital information system. MRI and DW-MRI were evaluated by two radiologists who had one year and ten years of experience in radiology with a consensus reading. Image interpretation was blinded to clinical information.

We used the largest lymphadenopathies (LAP) in the evaluation. Lymph nodes that are larger than 1 cm in the smallest diameter and without cystic or necrotic component on US reports, with high DW-MRI and low ADC signal on MRI, were defined as solid LAP. Necrotic LAP were considered the lesions which were defined as cavitary lesions on US reports and had low DW-MRI and high ADC signal on MRI (Figure 1-4). In homogenously enlarged lymph nodes (solid LAP), a region of interest (ROI) was placed inside the margins of the lesion to measure ADC value. When there was heterogeneity in signal intensity of the lesion, a larger ROI for whole lesion and two smaller ROIs were placed within both cystic-necrotic areas and areas which showed enhancement after gadolinium administration. Mean ADC values of regions with high and low ADC signals were calculated separately.

We made minimal ROI size determination based on parameters suggested before [10]. Minimal ROI size was equal or larger than the voxel size to prevent partial volume effect would not produce unreliable measurements. We calculated the voxel size of each DWI-sequence separately using FOV, matrix size, and slice thickness parameters. ROI size, which is smaller than this calculated voxel size, was not applied.

The signal intensities of the lesions on T2, DW-MRI and ADC map images were visually compared to the adjacent muscle using a 5-point scale system: 1: hypointense, 2: moderately hypointense, 3: isointense, 4: moderately hyperintense, 5: significantly hyperintense. Because the DW-MRI sequence had a low spatial resolution, borders of ROI were defined with the guidance of conventional MRI. We made the quantitative ADC measurements on ADC map images. Mean ADC values, which were measured by the same two radiologists, and the differences were decided with a consensus.

Statistical analysis

Quantitative variables are summarized with mean ± standard deviation values. Qualitative variables were compared with the Chi^2 test between the two groups. Because of continuous variables did not provide the assumption of normality, non-parametric Mann Whitney U test was used to compare the groups. We performed data analysis in SPSS 25.0 program (SPSS Inc., Chicago, Illinois, USA) and interpreted statistical tests at $p < 0.05$ significance level.

Results

In the tularaemia group (n: 32), there were 18(56%) solid, 14(44%) necrotic LAP. In the metastatic group (n: 27), there were 18(67%) solid and 9(33%) necrotic LAP. In the tularaemia group, 20(62%) of the patients were male, 12(38%) of the patients were female. In the metastatic group, 20(74%) of the patients were male, 7(26%) of the patients were female (Table 1). The mean age and age range of the patients in the tularaemia and metastatic groups were shown in table 2.

Table 1. Demographic information (sex).

Parameters	Metastatic	Tularemia	Total
Male	20	20	40
Female	7	12	19
Total	27	32	59

Table 2. Demographic information (age).

	Metastatic (27)		Tularemia (32)		Total (59)
	Solid (18)	Necrotic (9)	Solid (18)	Necrotic (14)	
Mean age	54,3	59	52,5	51,7	53,9
Age range	24-76	25-78	22-71	20-68	20-78

All necrotic LAP, regardless of tularaemia or metastatic group, showed peripheral contrast enhancement. In patients with solid LAP, we found homogeneous contrast involvement in 13 patients in the tularaemia group, 11 patients in the metastasis group, 5 patients in the tularaemia group, and 7 patients in the metastasis group. There was no significant difference between solid and necrotic LAP enhancement patterns in tularaemia and metastasis groups *(p>0.05)*.

T2 signal was high in all lesions, mostly in the central part of necrotic LAP. Solid LAP and peripheral parts of necrotic LAP showed high DWI and low ADC signal, whereas DWI and ADC signals of central parts of necrotic LAP were the opposite (Table 3-5).

Table 3. Qualitative mean MRI scores of tularemia and metastatic solid lymphadenopathies.

Sequence	Tularemia	Metastasis	*p*
T2WI	4.1	4	*0.923*
DW-MRI	4.8	4.66	*0.865*
ADC	1	1.22	*0.629*

There was no significant difference between tularaemia and metastasis groups in terms of qualitative signal characteristics.

Table 4. Qualitative mean MRI scores of tularemia and metastatic necrotic lymphadenopathies.

	Central			Peripheral		
	T2WI	DWI	ADC	T2WI	DWI	ADC
Tularaemia	5.0	2.71	5.0	3.93	4.54	2.3
Metastasis	5.0	2.27	5.0	3.72	4.81	2.18
p	*1.0*	*0.226*	*1.0*	*0.563*	*0.061*	*0.857*

In solid LAP patients, there was no significant difference between ADC measurements in tularemia and metastasis groups. In necrotic LAP patients, total, central and peripheral ADC measurements were significantly higher in the metastatic group than in the tularemia group. According to the ROC analysis, ADC cut-off values were found to be 1.915×10^{-3} mm^2/s (Sensitivity: 81.8%, Specificity: 78.6%, AUC: 0.799, p=0.012) for central portions of necrotic LAP, 0.815×10^{-3} mm^2/s (Sensitivity: 81.8%, Specificity:50%, AUC: 0.773, p=0.021) for peripheral portions of necrotic LAP and 1.345×10^{-3} mm^2/s (Sensitivity:90.9%, Specificity:78.6%, AUC: 0.851, p=0.003) for total part of necrotic LAP to differentiate metastatic and tularemia groups in necrotic LAP (Figure 5).

Discussion

We found that necrotic LAP had significantly higher ADC values in the metastatic group in comparison to tularaemia. Differentiation of malign LAP from tularaemia cases with head and neck involvement in MRI or DWI might not be possible and could cause a diagnostic dilemma. In this case, if the LAP is necrotic, ADC values have diagnostic value for differentiation of metastasis.

Table 5. Quantitative mean ADC values of tularaemia and metastatic lymphadenopathies.

	Solid (10^{-3} mm^2/s)	**Necrotic**		
		Total (10^{-3} mm^2/s)	**Central** (10^{-3} mm^2/s)	**Peripheral** (10^{-3} mm^2/s)
Tularemia	0.74 ± 0.05	1.21±0.21	1.76±0.44	0.80 ±0.05
Metastasis	0.76 ± 0.12	1.67±0.35	2.32±0.49	0.92± 0.20
P	*0.372*	*0.002**	*0.011**	*0.021**

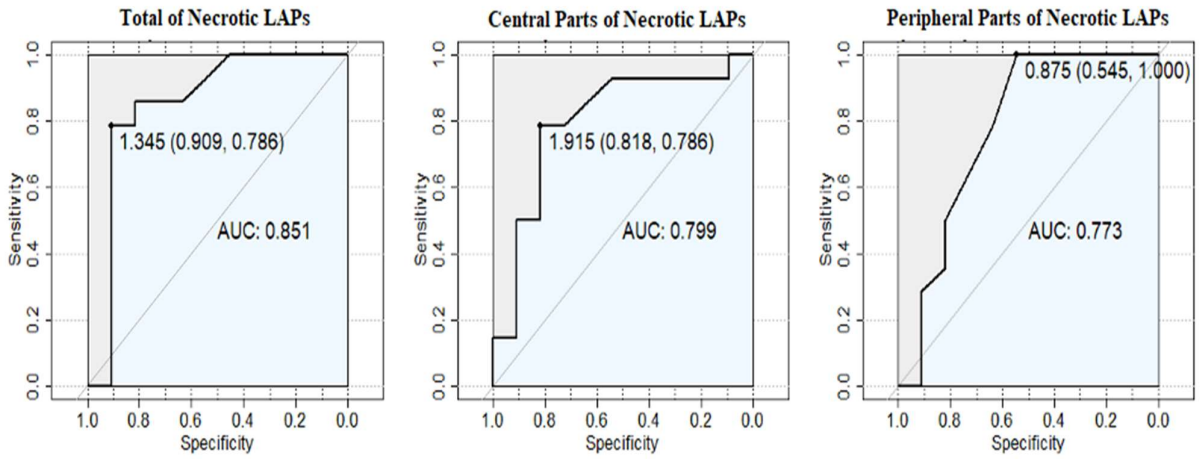

Figure 5. ROC analysis of ADC values according to total, central, and peripheral parts of necrotic LAP to discriminate tularaemia from metastasis.

In our study, both tularaemia and malignant solid LAP had low mean ADC values and were hypointense on ADC and had similar mean ADC values. In previous studies, the mean ADC values in metastatic LAP were reported as $0.59 \pm 0.27 \times 10^{-3}$ mm^2/s, $0.78 \pm 0.09 \times 10^{-3}$ mm^2/s, $0.85 + 0.27 \times 10^{-3}$ mm^2/s [12-14]. Furthermore, there are several reported cases of LAP with granulomatous reaction such as sarcoidosis and cat scratch disease, that present low ADC values resembling malignancy [10, 15, 16]. The reason for restricted diffusion in tularaemia might be the ability of the pathogen to impair phagocyte function, and thus survive in the infected cells [17].

We found that ADC and T2 signals were high in the central part of the necrotic LAP in both groups. This situation was also similar for metastatic necrotic LAP and contrary to necrotic lymphadenitis in the study of Koç et al. [18]. However, in qualitative evaluation, mean ADC values of central parts and the total of necrotic LAP were significantly higher in the metastatic group than the tularaemia group. When thresholds of mean ADC values were determined as 1.915×10^{-3} mm^2/s for the central part and 1.345×10^{-3} mm^2/s for the total of necrotic LAP, differentiation is probable with high sensitivity and specificity. Since necrosis is a factor that increases diffusion, ADC values of the peripheral solid parts of the necrotic LAP, which are viable, were similar to the ADC values of LAP without necrosis. However, diffusion increases in the necrotic parts,

regardless of emerging due to tularaemia or malignant causes [19]. In our study, central, peripheral, and total ADC values of necrotic LAP were significantly higher *(p=0.011)* in the metastatic group than in the tularaemia group by the quantitative ADC evaluation. Koç et al. reported that ADC values of tumoral necrotic lymph nodes were significantly higher than those of infective necrotic lymph nodes, and they attributed that the movement of water molecules was freer than infective necrosis with high protein content, as a reason of this. Whereas Koç et al. reported that infective necrotic lymph nodes were hyperintense in DWI, DWI was hypointense in the necrotic parts of LAP in tularaemia group in our study [18]. However, ADC values of tumoral necrotic LAP were significantly higher than necrotic LAP in tularaemia. This condition is thought to be related to the intense content with necrosis in tularaemia, and it can be used as a parameter to differentiate tularaemia-metastasis. However, considering that this situation may be due to the low number of our study population, studies with a larger population are needed on this subject.

Although the mean ADC values of the peripheral part of the necrotic LAP were also significantly higher in metastatic groups than the peripheral group, specificity was lower than the central parts or total of the necrotic LAP. This condition might be due to the effect of large central necrotic part of the LAP on the thin peripheral part in which ROI placed because of the low resolution of DWI.

There were certain limitations to this study. First, since a limited patient population might restrain the results, they should be confirmed on a larger scale. Second, US or fine-needle aspiration could not be performed by us, and we obtained the reports of these procedures from the archives. Third, we evaluate images with a consensus of two observers, so we did not assess interobserver variability.

Both tularaemia and metastases cause solid and necrotic LAP in the neck. Conventional MRI findings do not provide sufficient information to differentiate these lesions. There was no significant difference in tularaemia and tumour in terms of signal characteristics in solid LAP. Since tularaemia is an infectious disease, clinical findings might be considered useful in differentiation; however, confusing clinical presentation is not uncommon in tularaemia. Microagglutination test will be useful in the evaluation of these lesions. The microagglutination test might be used in necrotic LAP; however, despite tularaemia and tumour signal characteristics are similar, higher ADC values might favour the diagnosis of tumour in necrotic LAP than tularaemia and might be useful for differentiation and may expedite the diagnosis.

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Ethical statement: *This retrospective study was reviewed and approved by institutional ethical board. (Approval Date: 18.02.2020, Decision No: 2020/28).*

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