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Original Article

Diffusion weighted-MRI in distinguishing between tumor-like benign lympho-epithelial lesion and mucosa-associated lymphoid tissue lymphoma of parotid gland

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Abstract: Introduction: Benign lympho-epithelial lesion(BLEL)in the parotid gland is a common autoimmune disease, with a 44 times higher risk of lymphoma compared to the general population. 85% of lymphomas arising from BLEL in the parotid gland are mucosa-associated lymphoid tissue (MALT) lymphoma. Aim: It is often difficult to differentiate between a MALT lymphoma and a tumor-like BLEL in the parotid gland on MR images. The aim of this study was to determine if DWI-MR can differentiate MALT lymphoma from lymphoepthlial lesion in the parotid gland. Methods and materials: Twenty-four subjects with tumor-like BLEL and 19 subjects with MALT lymphomas in the parotid gland were included in this study. All subjects were confirmed by histo-pathology and preoperatively underwent DWI-MR at 1.5T MR units. The apparent diffusion coefficient (ADC) maps were constructed, and the ADC values of the lesions were calculated from DWI-MR (b = 500 s/mm^2 and 1000 s/mm^2). The difference between tumor-like BLEL and MALT lymphoma was analyzed by the Mann-Whitney test using the SPSS 18.0 software package. Results: Successful DWI-MR scans were acquired in 24 subjects with tumor-like BLEL (3 males, 21 females; mean age of 55.8 years) and 19 subjects with MALT lymphoma (6 males, 13 females; mean age of 52.5 years). The ADC map for MALT lymphomas was lower compared to the tumor-like BLEL map. The ADC value at b = 500 s/mm^2 could not be used to distinguish between MALT lymphoma from tumor-like BLEL, but can be used at b = 1000 s/mm^2. The $ADC_{b=1000}$ threshold of > 0.669×10^{-3} mm^2/s yielded a sensitivity, specificity, and accuracy of 78.9%, 95.8% and 88.4%, respectively. Conclusion: DWI-MR may be a valuable method in differentiating MALT lymphoma from tumor-like BLEL in the parotid gland.

Keywords: DWI-MR, tumor-like BLEL, MALT lymphoma, parotid gland

Introduction

Normal parotid tissues rarely contain mucosa-associated lymphoid tissue (MALT); however, if chronic inflammation in the parotid gland or autoimmune diseases such as benign lympho-epithelial lesion (BLEL) occur, lymphoid tissues might accumulate and proliferate, leading to acquired MALT lymphoma [1]. Research has found that amongst patients with BLEL, approximately 4%~7% developed lymphomas. The risk for the occurrence of lymphoma in this patient group is 44 times higher than that of the general population, of which 85% are MALT lymphomas. [2-4]. Parotid gland BLEL and MALT lymphoma are closely related, and therefore, timely and precise identification is important for treatment and prognosis estimation. Parotid BLEL is generally categorized as diffused, atrophied, tumor-like, and infectious types. The diffused, atrophied and infectious types lack solid lumps or nodules. Thus, they are easily distinguishable from parotid BLEL based on conventional imaging. However, tumor-like BLEL cannot be differentiated from MALT lymphoma by using regular computed tomography or magnetic resonance imaging (MRI) [5-6].

Diffusion weighted imaging (DWI) is currently the only imaging technology that can non-invasively reflect the motion of water molecules *in vivo* [7-9]. Its applications in studies of parotid tumors have been reported in recent years, and the results indicated that apparent diffusion coefficient (ADC) measurements are valuable to some degree in distinguishing between benign and malignant parotid tumors [10-11]. However, its application in distinguishing between parotid tumor-like BLEL and MALT lymphoma has yet not been reported.

The present study determined the mean ADC of parotid BLEL and MALT lymphoma when b value was 500 and 1000 s/mm^2, and analyzed the strength of using mean ADC obtained for two b values in distinguishing between the two lesions.

Materials and methods

Subjects

This retrospective study was approved by the Review Committee of Shanghai Ninth Hospital Affilicated to Shanghai Jiaotong University School of Medicine, and written informed consent was obtained from all the subjects. Twenty-five subjects with parotid tumor-like BLEL, and 20 subjects with parotid MALT lymphoma who visited our hospital from January 2003 to November 2013 were included. DWI could not be completed in one parotid tumor-like BLEL patient and one parotid MALT lymphoma patient because of oral metal artifacts. DWI failed in another parotid MALT lymphoma patient at b value = 500 s/mm^2, because of the patient's random movement during scanning. Twenty-seven subjects (27/45, 60%) complained of symptoms from Sjogren's syndrome, such as dry eyes and dry mouth, and 20 (20/45, 44.4%) complained of a swollen parotid gland, but without pain or facial paralysis. Nine subjects with tumor-like parotid BLEL and 11 with MALT lymphoma had a medium-sized palpable mass, which was slightly mobile, but did not cause tenderness, during the examination. This study followed the Declaration of Helsinki on medical protocol and ethics, and the regional Ethical Review Board of Shanghai Ninth's People's Hospital approved the study.

DWI-MR scanning

A 1.5-Tesla MR scanner (Sigma MR/I, GE medical System, Milwaukee, WI, USA) was used in this study, with head and neck array coils.

DW-MRI examinations were performed using a SE single shot echo-planar imaging (EPI) sequence in the transvers plane with a TR of 4,000 ms and TE of 51.8 ms. Sensitizing diffusion gradients were applied sequentially in the x, y, and z axis with b-values set at 500 or 1,000 s/mm^2. ADC maps were generated. Tumors were identified on the transverse T1-weighted MR images, and three sections (one section accounted for the maximum diameter of the tumor) were selected for DCE imaging. FSE T1-weighted images were obtained with a TR of 400-600 ms and a TE of 8-9.9 ms.

Determination of the region of interest (ROI)

All MR images were interpreted and a consensus was achieved by two radiologists (10-12 years of experience in head and neck MR imaging, respectively), who were blinded to clinical information and the histopathologic results. Functool 2 software was used to process DWI-MR data, and the steps included original image input, threshold optimization, background removal, and b value input.

Based on the morphology of thetumor in MR imaging, parotid tumor-like BLEL and MALT lymphoma were classified into solitary nodule type and multiple nodules type. The section with the maximum diameter or the highest number of nodules was selected as the central section, and additional sections 1.25 cm above and below were also selected. ROI was manually determined by connecting all relevant points, and covered the major lesion region as much as possible. The mean ADC value were calculated based on the corresponding values when b was set to 500 and 1000 s/mm^2 according to the result of two radiologists' measurement.

Statistical analysis

The mean ADC of the parotid tumor-like BLEL and MALT lymphoma, according to the measurements when b was set to 500 and 1000 s/mm^2, were subjected to the T test and the receiver operating characteristic (ROC) curve was constructed. The Youden index was used to determine the optimized threshold value,

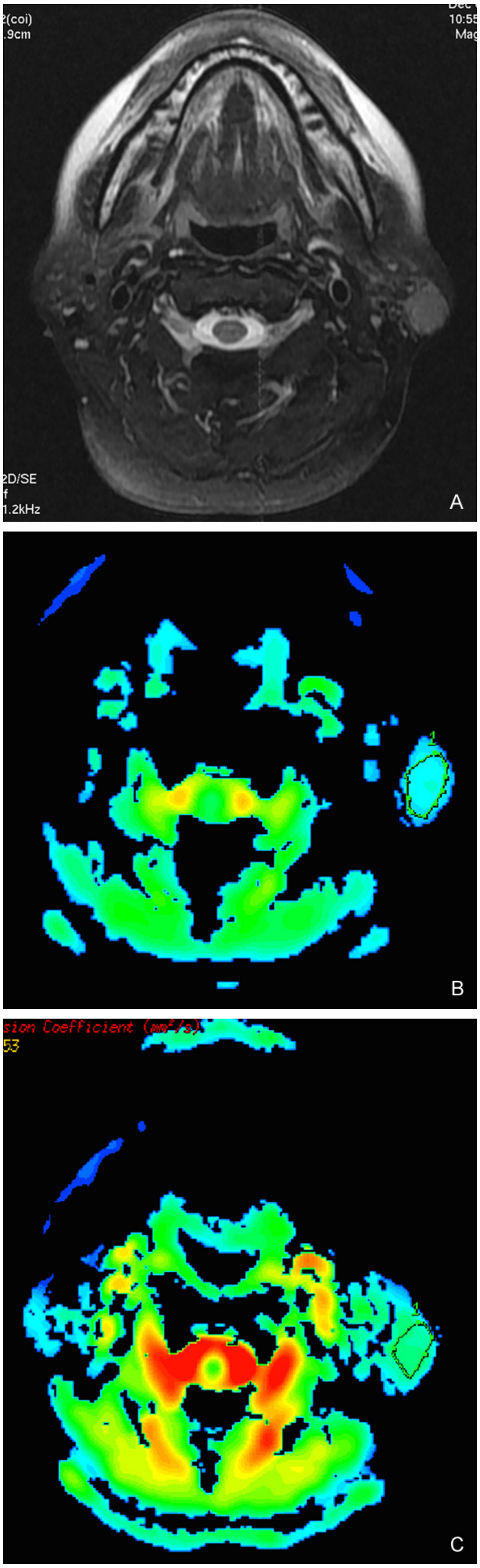

Figure 1. A. BLEL of the parotid gland (solitary nodule). B. ADC value was 1.09×10^{-3} mm^2/s (b = 500 s/mm^2). C. ADC value was 0.710×10^{-3} mm^2/s (b = 1000 s/mm^2).

which was further used to calculate sensitivity, specificity and accuracy. SPSS 10.0 statistical software package (SPSS, Chicago, IL, USA: 1999) was used and $P < 0.05$ was considered statistically significant.

Results

Subjects

Forty-three subjects underwent DWI-MR (b = 500 and 1000 s/mm^2), including 24 with parotid tumor-like BLEL (3 male, 21 female, aged 19-74 years, mean age of 55.8 years), and 19 with parotid MALT lymphoma (6 male, 13 female, aged 29-76 years, mean age of 52.5 years). All the subjects with parotid tumor-like BLEL completed ADC measurements at b = 500 and 1000 s/mm^2. Among the subjects with parotid MALT lymphoma, 18 completed ADC measurements at b = 500 and 1000 s/mm^2, and the remaining one only completed ADC measurement at b = 1000 s/mm^2.

Mean ADC at b = 500 s/mm^2

When b was set to 500 s/mm^2, we could not complete ADC measurement in one patient with parotid tumor-like BLEL, as well as two measurements in subjects with parotid MALT lymphoma, but measurement was completed in all the remaining subjects. Mean ADC of parotid tumor-like BLEL (**Figure 1A**) was 1.16×10^{-3} mm^2/s (**Figure 1B**), whereas, mean ADC of the parotid MALT lymphoma (**Figure 2A**) was 1.06×10^{-3} mm^2/s (**Figure 2B**). Statistical analysis did not detect any significant difference between the two groups ($P = 0.359$) (**Table 1**).

Mean ADC at b = 1000 s/mm^2

When b was set to 1000 s/mm^2, we could not complete ADC measurement in one patient with parotid tumor-like BLEL and in one parotid MALT lymphoma patient, but measurement was completed in all the remaining subjects. Mean ADC of parotid tumor-like BLEL was 0.992×10^{-3} mm^2/s (**Figure 1C**), whereas mean ADC of the parotid MALT lymphoma was 0.634×10^{-3} mm^2/s (**Figure 2C**). Statistical anal-

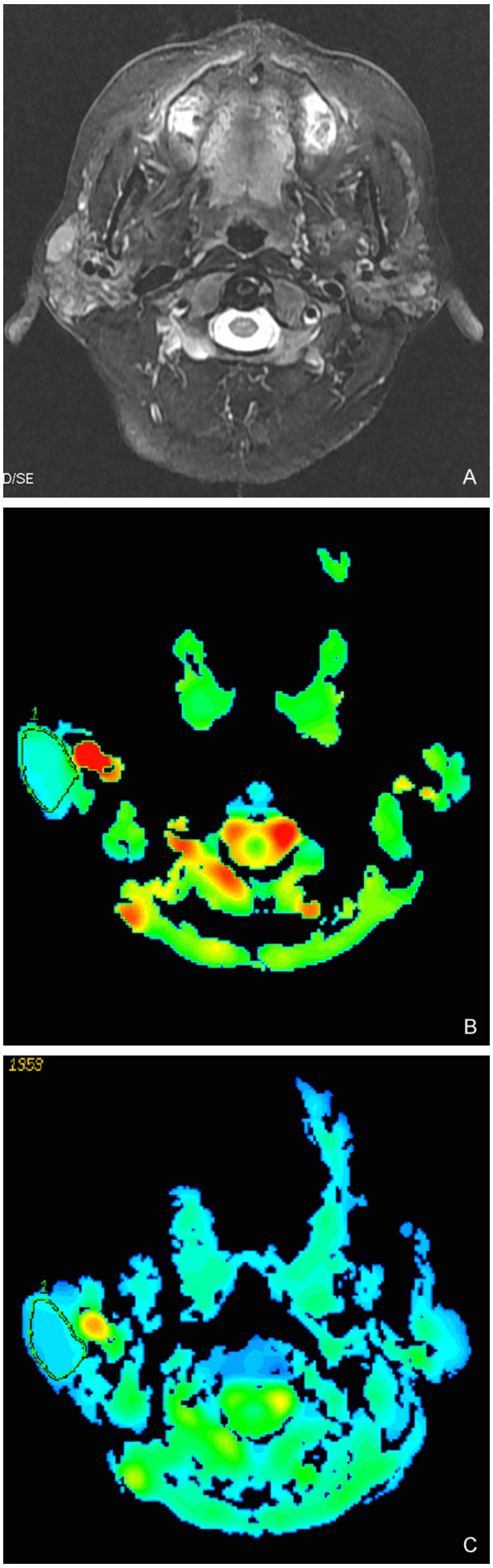

Figure 2. A. MALT lymphoma of the parotid gland (diffuse solid-cystic nodules or masses). B. ADC value was 0.722×10^{-3} mm^2/s (b = 500 s/mm^2). C. ADC value was 0.563×10^{-3} mm^2/s (b = 1000 s/mm^2).

ysis revealed a significant difference between the two groups (P < 0.001) (**Table 1**). The area under the ROC curve was 0.938, and the Youden Index suggested that the optimized threshold value was 0.669×10^{-3} mm^2/s (**Figure 3**). If ADC > 0.669 mm^2/s was considered parotid tumor-like BLEL (true negative) and ADC < 0.669 mm^2/s was considered parotid MALT lymphoma (true positive), there was 1 false positive, 4 false negative, 23 true-negative and 15 true-positive results. The measurement sensitivity was 15/19 (78.9%), specificity was 23/24 (95.8%), and accuracy was 38/43 (88.4%).

Discussion

DWI-MR in diagnosis of parotid tumor

Preliminary studies have suggested that different tumors have different ADC values. Hermann et al [12]. studied 45 cases with primary parotid gland tumors of seven different types and found that the ADC of Worthin's tumor was significantly lower than that of mucoepidermoid carcinoma, and the ADC of the latter was again significantly lower than that of pleomorphic adenoma. Worthin's tumor has many intercellular substances and small cysts, which cause irregular water motion and consequent low ADC value. Hermann et al [13]. studied 149 primary parotid gland tumors of 14 different types and found that among the four ADC values measured at different location (very low, low, intermediate, and high), the high was the most indicative in terms of distinguishing between benign and malignant tumors. ADC values of parotid pleomorphic adenoma and Warthin's tumor were 2.03×10^{-3}-2.14×10^{-3} mm^2/s and 0.89×10^{-3} mm^2/s, respectively, and the latter was lower than that of parotid malignant tumor (1.19×10^{-3} mm^2/s). Their study indicated that ADC value plus morphological results could be used to identify various primary benign and malignant parotid tumors.

In contrast, Matsushima [11] raised a question about the use of ADC values in distinguishing between benign and malignant parotid tumors.

Table 1. Mean ADC values of tumor-like BLEL and MALT lymphoma of the parotid gland

Group	b = 500 s/mm^2	b = 1000 s/mm^2
Tumor-like BLEL	1.16×10^{-3} mm^2/s	0.992×10^{-3} mm^2/s
MALT lymphoma	1.06×10^{-3} mm^2/s	0.634×10^{-3} mm^2/s
P value	0.359	< 0.001

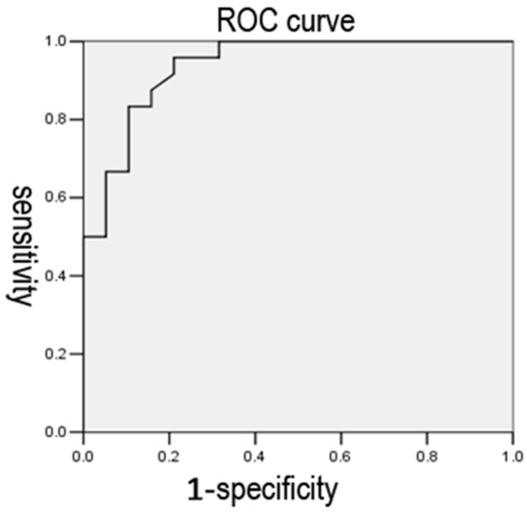

Figure 3. ROC of ADC values as b = 1000 s/mm^2.

He studied 32 cases of salivary tumors (17 benign and 15 malignant) and found that the ADC values did not differ significantly between them. However, the extracellular matrix content was correlated with the ADC value. Many studies have found that although the ADC values are lower in malignant salivary tumors when compared with benign tumors, the ADC values of Worthin's tumor was even lower than those of malignant tumors.

Diagnostic value of mean ADC at b = 500 s/mm^2

The present study found that when b was set at 500 s/mm^2, the mean ADCs of the parotid tumor-like BLEL and parotid MALT lymphoma were 1.16×10^{-3} and 1.06×10^{-3} mm^2/s, respectively. The possible explanation was that during the transition of BLEL to MALT lymphoma, lymphatic cells continuously aggregated and the proportion of the cystic contents in the lesion decreased. However, statistical analysis found that at b = 500 s/mm^2, the mean ADC of the parotid tumor-like BLEL and parotid MALT lymphoma did not differ significantly. Therefore, ADC value at b = 500 s/mm^2 could not be used to distinguish between the two types of tumor.

Diagnostic value of mean ADC at b = 1000 s/mm^2

When b was set to 1000 s/mm^2, the mean ADCs of the parotid tumor-like BLEL and parotid MALT lymphoma were 0.992×10^{-3} and 0.634×10^{-3} mm^2/s, respectively. Both were lower than the corresponding values with b = 500 s/mm^2. However, as when b was set at 500 s/mm^2, the former was slightly higher than the latter. The reason might be that during the transition of BLEL to MALT lymphoma, lymphatic cells continuously aggregated and the proportion of the cystic contents in the lesion decreased. Statistical analysis found that at b = 1000 s/mm^2, the mean ADC of the parotid tumor-like BLEL and parotid MALT lymphoma were significantly different. Therefore, ADC value at b = 1000 s/mm^2 provided useful information and might be applied to distinguish between the two types of tumors. If ADC > 0.669×10^{-3} mm^2/s was considered the threshold, the sensitivity, specificity, and accuracy distinguishing between the parotid tumor-like BLEL and the parotid MALT lymphoma were 78.9%, 95.8% and 88.4%, respectively. We concluded that such a threshold was highly accurate if used to diagnose the parotid tumor-like BLEL, and was better than when used to diagnose the parotid MALT tumor. The overall accuracy was 88.4%.

Effects of different b values on distinguishing between parotid tumor-like BLEL and MALT lymphoma

In the present study, we set b1 to 500 s/mm^2 and 1000 s/mm^2, respectively, and b2 to 0, which was a default (in the following discussion, b value means b1, and b2 is 0).

Literature review [14-17] showed that during head and neck DWI, b was always set to 500 or 1000 s/mm^2. The present study found that at b = 1000 s/mm^2, the mean ADCs of the parotid tumor-like BLEL and parotid MALT lymphoma were 0.992×10^{-3} and 0.634×10^{-3} mm^2/s, respectively; both lower than 1.22×10^{-3} mm^2/s (mean ADC of the benign tumor was more than 1.22×10^{-3} mm^2/s). The possible explanation was that they both contained small cysts as well as a large amount of intercellular substance, which could affect the water motion, causing water diffusion and a lower ADC value. Therefore, mean ADC could be used to distinguish between the parotid tumor-like BLEL and parotid MALT lymphoma and other primary benign parotid gland tumors. However, at b = 500 s/mm^2, mean ADC could not be used to distinguish between the parotid tumor-like BLEL and parotid MALT lymphoma. At b = 1000 s/mm^2, the ADC of the parotid MALT lymphoma was significantly lower than that of the parotid tumor-like BLEL and therefore mean ADC could help distinguish between them. Instead, the mean ADC of the parotid MALT lymphoma was 0.634×10^{-3} mm^2/s, which is consistent with that reported by Wang et al [18], who showed that head malignant lymphoma had the lowest mean ADC (0.66×10^{-3} mm^2/s).

Limitations of DWI-MR

Different organs require different b values: for example, 1000-2000 s/mm^2 for brain and 165 s/mm^2 for vertebral bodies. Therefore, ADC valuesofthe same lesions in different organs are not comparable, which limits the clinical useof DWI.

Additionally, ROI selection was not standardized. Some researchers believe that ROI should be limited to solid masses without any cysts or calcification. However, we believe that many head and neck primary tumors, whether or not they are cystic or solid, reflect the pathological status of the lesions. The presence of cysts could also affect the diffusion direction and magnitude of the water molecules, and consequently, should not be excluded from the ROI. Calcified and bleeding regions over-affected the ADC values. Meanwhile, calcification and bleeding are not the typical manifestations of the parotid tumor-like BLEL and parotid MALT lymphoma, and therefore were not included in the ROI. The present study selected the maximum section and the sections above and below, for a total of three sections for the measurements. We did not include the entire lesion region, thus, whether the results reflected the actual lesion situation, how to select better sections, and how to determine the ROI that reflects the entire lesion, need further investigation.

The present study found the correlation between mean ADC and malignancy of the parotid tumor-like BLEL and parotid MALT lymphoma. However, the study did not take malignancy into account during analysis. Therefore, further improvements are needed.

Conclusion

The present study found that parotid tumor-like BLEL had a lower mean ADC than head and neck malignant tumors, which was 1.22×10^{-3} mm^2/s, at b = 500 and 1000 s/mm^2, indicating that BLEL, like Worthin's tumor, was a benign tumor with a large amount of lymphoid intercellular substances. Parotid MALT lymphoma had a similar mean ADC as the head and neck malignant lymphoma (malignant lymphoma had the lowest ADC among all malignant tumors), at b = 500 and 1000 s/mm^2, indicating that the malignancy of the MALT lymphoma was low grade, but the lymphoid intercellular substance content was high. At b = 1000 s/mm^2, parotid tumor-like BLEL and parotid MALT lymphoma were significantly different, and the corresponding mean ADC values could be used for distinguishing between them.

In summary, DWI-MR provided important information that could be used to distinguish between parotid tumor-like BLEL and parotid MALT lymphoma during diagnosis. Such information is important in the subsequenttreatment protocol, determination, and prognosis evaluation.

Disclosure of conflict of interest

None.

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