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ORIGINAL ARTICLE

Orbital Lymphoma; A Search for MRI Predictors of Disease Extent and Treatment Response

Orbital Lenfoma; Hastalık Yaygınlığı ve Tedaviye Cevabın Manyetik Rezonans Görüntüleme Belirteçlerinin Araştırılması

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ABSTRACT

Objective: Lymphoma is the most common orbital malignancy in adults. We aimed to investigate pretreatment MRI predictors of systemic involvement and early therapy response.
Material and Methods: Histopathologically confirmed orbital lymphoma patients with MRI scans at the time of diagnosis and after treatment constituted the study group. Involvement of lacrimal gland, intraconal and extraconal fat, eyelid, optic nerve and/or optic nerve sheath, extraocular muscles, intraocular involvement and presence of bone destruction were evaluated from pretreatment MR scans by two radiologists. Involvement of orbital structures were compared in systemic and localized disease. Measurements of ADC values of the mass and pons were collected and the ratio (rADC= lymphoma ADC/ pontine ADC) was calculated. Response to treatment was evaluated from the follow-up MR images.
Results: Twenty patients (F/M= 10/10, mean age 57.3 ± 19.7) constituted the study group and histopathologic diagnosis was predominantly B cell lymphoma, extranodal marginal zone lymphoma being the most common (n=12, 60%). The most commonly involved structures were extraconal fat tissue (70%), lacrimal gland (50%) extraocular muscles (40%). Intraconal fat involvement was significantly higher (p=0.017) in patients with systemic disease compared to localized disease. rADC values showed no difference between patients with systemic and localized disease or patients with complete or partial response (p>0.05).
Conclusion: Intraconal fat involvement of orbital lymphoma could predict a systemic disease. The predictive value of pretreatment ADC levels should be searched in larger future cohorts.

Keywords: Orbital lymphoma, MRI

ÖZ

Giriş: Lenfoma erişkinlerde en sık görülen orbital malignitedir. Bu çalışmada orbital lenfomda sistemik tutulumun ve tedaviye cevabın tedavi öncesindeki manyetik rezonans görüntüleme (MRG)'deki belirteçlerini araştırmayı hedefledik.
Gereç ve yöntemler: Tedavi öncesinde ve takipte MR görüntülemesi olan, histopatolojik olarak doğrulanmış orbital lenfoma tanısı olan hastalar çalışma grubunu oluşturdu. Tedavi öncesi MRG'den lakrimal bez, ekstrakonal ve intrakonal yağ dokusu, optik sinir ve/veya optik sinir kılıfı, ekstraoküler kas tutulumları, intraoküler yayılım ve kemik destrüksiyon varlığı iki radyolog tarafından değerlendirildi. Sistemik ve lokalize hastalıkta orbita içi yapıların tutulumları karşılaştırıldı. Ponstan ve kitleden ADC (apparent diffusion coefficient) ölçümü yapıldı ve oranları (rADC= lenfoma ADC/ pons ADC) hesaplandı. Tedaviye cevap takip MRG'den değerlendirildi.
Bulgular: Yirmi hasta (K/E= 10/10, ortalama yaş 57.3 ± 19.7) çalışma grubunu oluşturdu. Histopatolojik tanı baskın olarak B hücreli lenfoma olup, ekstranodal marjinal zon lenfoma en sık görülen türdü (n=12, %60). En sık tutulan yapılar extrakonal yağ dokusu (%70), lakrimal bez (%50) ve ekstraoküler kaslardı (%40). İntrakonal yağ dokusu tutulumu sistemik tutulumu olan hastalarda lokalize hastalığı olan hastalara hastalığı olan hastalara göre anlamlı olarak daha yüksekti (p=0.017). rADC değeri sistemik veya lokalize hastalığı olan hastalar ile tedaviye tam veya parsiyel yanıt gösteren hastalar arasında anlamlı farklılık göstermedi (p>0.05).
Sonuç: Orbital lenfomada intrakonal yağ dokusunun tutulumu sistemik tutulumun bir belirteci olabilir. Tedavi öncesi ADC değerinin yeri ise daha geniş ölçekli çalışmalarla araştırılmalıdır.

Anahtar kelimeler: Orbital lenfoma, MRG

Introduction

Lymphomas are a heterogeneous group of malignant tumors arising as clonal expansions of B-lymphocytes, T-lymphocytes or NK-cells (1). The most common orbital malignancy is lymphoma and constitutes 55% of adult malignant orbital tumors (2). The most common types of orbital lymphoma are B-cell origin and consists of extranodal marginal zone B-cell lymphoma (EMZL), diffuse large B-Cell lymphoma (DLBCL), follicular lymphoma (FL) and mantle cell lymphoma (MCL) (3). T-cell and NK-cell lymphomas are rare in the orbits (3). Diagnosis of orbital lymphoma includes orbital imaging followed by histopathologic evaluation of the tumor. Magnetic resonance imaging (MRI) provides high resolution images and helps determining the extent and location of the tumor, as well as the involvement of nearby structures. Lymphomas usually appear hyperdense on computerized tomography (CT) and avidly enhances after contrast material administration. Likewise, highly cellular lymphomas appear hypointense on T1 and T2 weighted (W) images on MRI. Significant enhancement after contrast material administration is also present on MRI. Bony destruction or perineural spread may suggest an aggressive histology (4). Additionally, diffusion weighted imaging (DWI) also helps in differentiating lymphomas from benign or other malignant diseases of the orbit (5–9).

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In this retrospective study, we aimed to seek any relation between localization and extent of the disease. We also sought for a relationship between localization of the disease, pretreatment apparent diffusion coefficient (ADC) values and initial response to therapy.

Material and Methods

This retrospective study was approved by the institutional review board (GO-20/661) and informed consent was waived. We retrospectively investigated the hospital information system from January 2015 to August 2020 for patients who underwent orbital MRI with the suspicion of lymphoma.

The inclusion criteria were set as 1) Histopathologically proven diagnosis of lymphoma involving the orbit, 2) Orbital MRI before the initiation of therapy, 3) Patients with >18 years old, 4) Follow-up MRI at 4-12 months after initiation of therapy. Exclusion criteria were set as: 1) Orbital MRI without diffusion weighted imaging.

Patient's demographic findings, precise histopathological diagnosis and presence of any other systemic involvement were recorded from the hospital archive system.

Images were collected from different vendors with 1.5 T magnetic field strength, including Aera (Siemens Healthcare, Germany), Achieva (Philips, Netherlands) and Signa Explorer (GE Healthcare, US). All of the MRI scans included axial and coronal T2 weighted (W) images, axial and coronal T1W images prior to and after intravenous contrast material injection and diffusion weighted images (DWI). Two radiologists evaluated the MRI scans. Involvement of orbital structures, i.e., lacrimal gland, intraconal and extraconal fat, eyelid, optic nerve and/or optic nerve sheath, extraocular muscles, intraocular involvement and presence of bone destruction were noted with consensus. Laterality of involvement was also investigated. Two radiologists measured ADC values independently by drawing region of interests (ROI) covering the center of the mass at the level of its largest diameter r on a single slice. ADC values at the center of the pons through the level of trigeminal nerve roots were also collected by the same radiologists, separately. Because the images were performed on different vendors, ratio of the mass to pons was calculated (rADC=lymphoma ADC/ pontine ADC).

Follow up MR images were also collected and time interval between the initial and follow up study was noted. Response to therapy was evaluated from the follow up MRI scans as complete and partial response. Complete response meant no mass with/without therapy associated signal changes with no mass effect and diffusion restriction. Partial response meant despite a decrease in size, a lesion creating mass affect and/or diffusion restriction was still present.

Statistical analysis was performed with the SPSS 25.0 package program. Depending on the type of variables (continuous vs. categorical), comparison tests was performed using Chi-squared test or Mann Whitney-U tests. Intraclass correlation coefficient (ICC) was used to evaluate interobserver agreement. The level of significance was 0.05 in all tests.

Results

Retrospective investigation of the hospital archive system revealed 40 adult patients. Two of them had MRI scans after the initiation of therapy, 12 patients had no DWI, 6 patients had no follow up MRI scans; therefore, a total of 20 patients were excluded from the study. Mean time interval between initial and follow up MRI scans was 177 ± 76 days.

Twenty patients (F/M= 10/10, mean age 57.3 ± 19.7) constituted the study group. Histopathologic diagnosis revealed B cell lymphoma predominantly (n=19) except for one patient who was diagnosed with T lymphoblastic lymphoma (5%). Majority of B cell lymphomas were low grade B cell lymphomas, i.e., EMZL (n=12, 60%), MCL (n=2, 10%), and FL (n=1, 5%). The other B cell lymphomas were high grade B cell lymphoma (n=2, 10%) and DLBCL (n=2, 10%). Eleven patients had disease localized to the orbits, all of them had B-cell lymphomas. However, 8 patients with B-cell lymphoma and one patient with T-cell lymphoma had systemic disease, including bone marrow involvement (n=4), systemic lymphadenopathies (n=4), pleural mass (n=1) and dura involvement (n=1). One patient had both bone marrow involvement and lymphadenopathies.

Review of MR images revealed that the most commonly involved orbital structure was extraconal fat tissue (n=14, 70%). Lacrimal gland involvement was present in 10 (50%) patients. None of the patients had intraocular disease. Table 1 summarizes the distribution of location of the disease in the orbita. Bilateral presence of disease was seen in 6 patients. Complete response was present in 13 patients and partial response was seen in 6 patients. One patient had complete metabolic response on metabolic imaging 2 months after the initiation of therapy, but had recurrent disease on his MRI 6 months later, therefore, could not be included in any response group. Further investigations revealed no difference between patients with localized and systemic disease in terms of orbital mass localization except for the intraconal fat. Intraconal fat involvement was significantly higher (p=0.017) in patients with systemic disease (n=6) compared to localized disease (n=1). When patients were grouped according to therapy response (complete vs partial) (n=19), involvement of intraconal fat tissue significantly differed between groups (p=0.010). Two of 13 patients (15.4%) with complete response had intraconal fat involvement, whereas 5 of 6 patients (83.3%) in the partial response group had intraconal fat involvement. On the other hand, involvement of extraocular fat (p=0.605), lacrimal gland (p=0.628), extraocular muscles (p=0.319), optic nerve/optic nerve sheath (p=0.557) or eyelid (p=0.262), presence of bone destruction (p=1.000) or systemic/ localized disease (p=0.057) had no difference between partial/complete response groups (Table 2). Mean ROI size for collecting ADC values was 0.46 ± 0.38 cm2. Interobserver agreement was excellent with ICC 0.982. As the ICC was excellent, measurements of

the first radiologist were used for further investigations. Median ADC value of lymphoma and pons were 0.631 (0.544- 0.738) x 10-3 mm2/s and 0.765 (0.704-0.840) x 10-3 mm2/s, respectively. Median rADC value was 0.86 (0.69-0.96). No difference of rADC values were detected between systemic and localized disease or complete and partial response groups (p>0.05) (Fig.1) (Table 3).

Table 1. Imaging Evaluation of Patients

	present
Extraconal fat tissue	14 (70%)
Lacrimal gland	10 (50%)
Extraocular muscles	8 (40%)
Intraconal fat tissue	7 (35%)
Optic nerve/optic nerve sheath	4 (20%)
Eyelid	6 (30%)
Bone destruction	3 (15%)

Table 2. Relation of disease extent and involvement of orbital structures with response to therapy.

Partial (n)		Response to therapy Complete (n)		p
Intraconal fat	absent	1	11	0.010*
	present	5	2	
Extraconal fat	absent	1	5	0.605
	present	5	8	
Lacrimal gland	absent	2	7	0.628
	present	4	6	
Extraocular muscles	absent	2	9	0.319
	present	4	4	
Optic nerve/Optic nerve sheath	absent	4	11	0.557
	present	2	2	
Bone destruction	absent	6	11	1.000
	present	0	2	
Eyelid	absent	3	11	0.262
	present	3	2	
Disease extent	systemic	1	9	0.057
	localized	5	4	

*statistically significant (p<0.05).

Table 3. rADC values of different groups.

	Systemic disease (n=9)	Localized disease (n=11)	Complete response (n=13)	Partial response (n=6)
rADC	0.85 (0.63-0.97)	0.87 (0.74-0.97)	0.89 (0.76-0.98)	0.81 (0.67-0.91)
p	0.603		0.416	

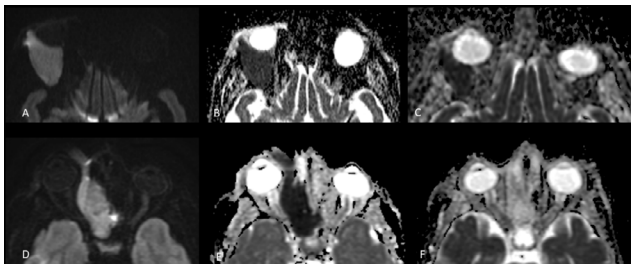

Fig1. Upper raw shows 86-year-old male diagnosed with mantle cell lymphoma infiltrating intra/extraconal fat tissue and lateral rectus muscle (A and B, arrows). Pretreatment DWI shows restricted diffusion in the mass (A and B) with partial response to therapy (decreased in size but still restricted diffusion) after 4 months (C, arrow). Lower raw shows 62-year-old female patient diagnosed with mantle cell lymphoma, infiltrating extraconal fat tissue, medial rectus muscle, extending to ethmoid air cells (D and E, arrows). Pretreatment DWI shows significant restriction in the mass which extends into paranasal sinus (D and E). ADC maps 5 months after initiation of therapy shows complete resolution of the mass with no restricted diffusion (F, arrow).

Discussion

In our cohort, the most common type of orbital lymphoma was EMZL and extraconal fat tissue was the most frequently involved site in the orbita. Intraconal fat was significantly involved in patients with systemic disease compared to patients with localized disease. It was also more common in patients with partial response compared to patients with complete response.

Extranodal marginal zone lymphoma was the major diagnosis constituting 60% in our cohort. This finding was consistent with larger cohorts supporting EMZL as the most common type of orbita lymphoma (51-59%) (2,3). Frequency were similar (10%) in our cohort. Frequency of FL, DLBCL and MCL were 5-22 % in larger cohorts (2,3). However, There was only one case of T-cell lymphoma (5%), which was found up to 3% of orbital lymphomas (3). Despite the small size, we might suggest that our cohort might represent the true frequencies of orbital lymphoma subtypes. Extraconal fat tissue was known the most commonly involved site for both B-cell and T-cell lymphomas (3), like in our cohort. Although T-cell lymphomas might be localized to extraocular muscles more frequently compared to B-cell lymphomas (3), we could not make any comparison due to limited number of cases, especially T-cell lymphomas.

Systemic involvement was present in 8 B-cell and 1 T-cell lymphoma. The only significant difference between localized and systemic disease was the involvement of intraconal fat. However, all of the patients with intraconal fat involvement had at least extraconal fat and/or extraocular muscles involved. So, intraconal fat involvement might also show the extent of the disease in the orbita, too. Besides, intraconal fat involvement was also significantly higher in partial response group compared to complete response group. As our cohort is relatively small, the relation of intraocular fat involvement with disease extent and response to therapy warrants further investigations.

Diffusion weighted imaging (DWI) can be useful in monitoring response to treatment, as well as diagnosis in orbital lymphoma patients (10,11). Our results showed that ADC values had no difference between complete or partial response groups. Although it's well-known that a lower DWI is related with higher cellularity, a previous study of orbital lymphomas suggested a better initial response in orbital lymphomas with lower ADC values (11). However, the study had a very short time interval (40-60 days) compared to ours, to define the response on MRI. On the other hand, another study suggested that a rise in ADC values early in the course of treatment might help to predict the treatment response. However, all of the studies, including ours, had limited number of patients and these findings had to be investigated with larger cohorts.

Our study had several limitations. The most important one is limited number of patients. Also due to the retrospective design of the study, the images were obtained by MR scanners from different vendors. Therefore, to overcome possible inhomogeneity of mean ADC values, we also calculated mean ADC ratios for each patient. Another limitation was the range of time interval between initial and follow-up scans. Due to retrospective design, we had to evaluate the treatment response in a wide range of time (4-12 months). Further studies should be designed with follow up scans at certain time intervals.

To summarize, our study confirms the extraconal fat as the most common location of orbital lymphoma. We also suggest that intraconal fat involvement could be used as a predictor of systemic involvement and might be a marker for response to therapy. ADC ratios at the time of diagnosis had been found to have no effect on predicting treatment response. However, further studies with larger cohorts are needed.

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Author Contributions

Ekim Gumeler: Conception, Design, Materials, Data collection, Analysis, Literature Review, Writer

Elif Bulut: Conception, Design, Supervision, Data Collection, Critical Reviwew

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