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Primary extranodal Non-Hodgkin lymphoma of the orbital and paranasal region—A retrospective study

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ABSTRACT

Purpose: Primary extranodal lymphomas of the orbit and sinonasal region are rare and occur almost only as Non-Hodgkin lymphoma (NHL). The purpose of this study was to determine the frequency of different subtypes of NHL in these regions and to describe their radiological features.
Materials and methods: Between January 2005 and January 2010, 567 patients with malignant immunoproliferative diseases (MID) were treated at our institution. Primary sinonasal and orbital manifestation was diagnosed in 36 cases. There were 13 women and 23 men with a median age of 67 years. CT and MRI were performed in 14 and 24 patients, respectively. Imaging was re-interpretated and histological subtypes were listed.
Results: Among all MID primary sinonasal and orbital NHL occurred with a frequency of 6%. Diffuse large cell lymphoma was identified in 11 cases (30%), marginal cell lymphoma in 6 (16%), and extranodal plasmacytoma in 5 (14%). Other subtypes were rare. On CT, lesions of soft tissue attenuation with homogeneous moderate contrast enhancement were seen in all cases. On T2-weighted fat saturated images 52% of the lesions were slightly hyperintense in comparison to unaffected musculature, 41% were isointense, and 7% slightly hypointense. On T1-weighted sequences most lesions (81%) were homogeneously isointense. After contrast administration marked enhancement was seen in 41%, moderate in 52%, and slight enhancement in 7%.
Conclusion: The identified radiological features should be included in the differential analysis of lesions in the orbital and sinonasal regions, but they are not specific enough. For exact therapeutic planning histopathological diagnosis of the subtype is required.

1. Introduction

Non-Hodgkin lymphoma (NHL) is the second most common neoplasm of the head and neck region [1–4]. However, only in a small number of cases it occurs as extranodal disease [2,3,5] with different subtypes (Table 1). The orbit and the sinonasal region are a rare site of origin. That is why it is difficult to determine the true frequency [2]. While pathological and clinical manifestations have been well documented, radiological literature comprises mainly case reports or smaller series, often performed with computed tomography (CT) [6,7]. In a few studies the appearance on magnetic resonance imaging (MRI) has been analyzed [8–10].

The purpose of this study was to determine the frequency of primary extranodal orbital and sinonasal lymphomas and their subtypes in our patient population and to describe their radiological features.

2. Material and methods

This retrospective study has been approved by the Institutional Ethics Committee.

Between January 2005 and January 2010, 567 patients with different malignant immunoproliferative diseases (MID) were treated at our institution. They included 364 patients with NHL, 41 patients with Hodgkin's disease, and 162 patients with multiple myeloma/plasmacytoma. The patients were identified by a retrospective analysis of medical records. Only those patients were included into this study who underwent complete initial staging work-up consisting of thorough clinical examination, complete haematological examination, bone marrow examination, radiological imaging including appropriate CT and/or MRI.

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Table 1
Histological subtypes of extranodal NHL in the sininasal/orbital region according to literature [1–4].

B cell NHL	T cell NHL
Follicular lymphoma	Lymphoepithelioid lymphoma
Mantle cell lymphoma	Angiocentric T/NK cell lymphoma
Marginal zone lymphoma (MALT-type)	Lymphoblastic lymphoma
Diffuse large cell lymphoma	
Lymphoblastic lymphoma	
Burkitt lymphoma	
Plasmablastic lymphoma	
Extramedullary plasmacytoma	

In 36 of 567 patients with MID primary extranodal orbital and sinonasal lymphoma was diagnosed. There were 13 women and 23 men with a median age of 67 years (range 9–84 years).

CT was performed as contrast enhanced spiral CT on a multidetector device (Somatom Sensation 64, Siemens, Germany) in 14 patients with the following parameters: 120 kVp, 150–200 mAs, collimation of 64 × 0.6 mm, pitch of 0.8 mm, primarily reconstruction interval of 0.4 mm, 100–120 ml intravenous contrast medium, flow rate of 2.0 ml/s. 2–3 mm thick axial and coronal multiplanar reconstructions (MPR) were obtained with bone and soft tissue kernel.

In 24 patients, MRI was performed using a 1.5 T MRI device (Magnetom Vision Sonata Upgrade, Siemens, Germany). The protocol included coronal T2-weighted (T2-w) fast spin echo sequence, axial fat-supressed T2-w short tau inversion recovery (STIR) sequence, and axial and/or coronal T1-w spin echo (SE) sequence. In all patients axial and coronal T1-w SE and/or T1-w SE fat-suppressed (FS) sequences were performed after intravenous administration of a paramagnetic contrast medium with a dose of 0.1 mg/kg. The slice thickness ranged between 3 and 5 mm.

All images were available in digital form. They were reinterpreted on a visual-qualitative basis by two radiologists (A.S. and S.K. with 8 and 25 years of experience, respectively) in consensus considering the following features: localisation, number of manifestations, signal intensity alterations, homogeneity and contrast enhancement (low, moderate, marked), bony changes (none, lytic, permeative, bone remodelling).

In all patients the diagnosis was confirmed by incisional biopsy. Histological subtypes of lymphomas obtained by haematoxilin/eosin stained sections and immunohistochemistry were listed. Furthermore, medical records were analyzed regarding the initial symptoms.

For statistical analysis the SPSS statistical software package was used (SPSS 17.0, SPSS Inc., Chicago IL, USA). Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Categorical variables were expressed as percentages. Patient specific outcomes were analyzed by Mann-Whitney-*U* test. Analyses of lesion specific outcomes were performed by means of generalized linear mixed models. $p < 0.05$ was taken to indicate statistical significance in all instances.

Table 2
Subtypes and localisations of identified primarily extranodal NHL ($n = 36$).

Type of NHL	Sinonasal region ($n = 13$)	Orbita ($n = 23$)
Follicular lymphoma	0	1 (4%)
Diffuse large cell lymphoma	4 (30%)	7 (30%)
Mantle cell lymphoma	1 (8%)	3 (13%)
Marginal cell lymphoma	1 (8%)	5 (22%)
Precursor B-cell lymphoma	0	2 (9%)
T-/NK-cell lymphoma	2 (15%)	0
MALT lymphoma	1 (8)	2 (9%)
Plasmacytoma	3 (23%)	2 (9%)
Burkitt lymphoma	1 (8%)	0
Unspecified cell lymphoma	0	1 (4%)

3. Results

All identified 36 patients with a primary orbital or sinonasal lymphoma suffered from NHL. The following subtypes could be noted: diffuse large cell lymphoma in 11 cases (30%), marginal cell lymphoma in 6 (16%), extranodal plasmacytoma in 5 (14%), mantle cell lymphoma in 4 (11%), mucosa associated lymphatic tissue (MALT) lymphoma in 3 (8%), precursor cell lymphoma in 2 (6%), T-/NK-cell lymphoma in 2 (6%), follicular cell lymphoma, Burkitt lymphoma and unspecified cell lymphoma in one case (3%), respectively. 23 (64%) primarily extranodal lymphomas originated in the orbit. In 13 cases (36%) the sinonasal area was the primary site (maxillar sinus, 8; frontal sinus, 1; sphenoidal sinus, 4). Localisation and subtypes are presented in Table 2. Related to all identified cases with MID at our institution the frequency of primarily extranodal sinonasal/orbital lymphomas was 6% with a varying percentage of subtypes between 0% and 11% according to international classification of diseases (Table 3).

Patients complained of nasal obstruction ($n = 9$), epistaxsis ($n = 4$), painless face swelling ($n = 15$), exophthalmos ($n = 5$), double-vision ($n = 4$), blurred vision or decreased visual acuity ($n = 4$).

On CT lesions of soft tissue density with homogeneous slight to moderate contrast enhancement were found in all instances.

On T2-w images with FS most lesions (59%) were slightly hyperintense in comparison to unaffected orbital/pterygoid musculature (Table 4). The hyperintensity was less prominent on T2-w images without FS. On T1-weighted sequences most lesions ($n = 22$, 71%) were homogeneously isointense in comparison to the orbital/pterygoid muscles (Figs. 1–4). After intravenous administration of gadolinium contrast medium marked or moderate enhancement was seen in 96% of the cases. It was homogenous in 16 (67%) and inhomogenous in 8 (33%) cases (Figs. 1–4).

Bone destruction was seen in 11 (31%) patients, all of them with sinonasal NHL. Additional regional lymphadenopathy occurred in 7 (19%) cases.

There were no differences between imaging patterns in several NHL subtypes (Table 5).

Table 3
ICD of primarily orbital/sinonasal lymphomas (POSL) in dependence of all identified malignant immunoproliferative diseases (MID).

Diseases, ICD 10	MID (n)	POSL (n)	POSL frequency (%)
ICD 81 (Hodgkin's disease)	41	–	–
ICD 82 (follicular NHL)	43	1	2
ICD 83 (diffuse NHL including MALT lymphoma, marginal cell lymphoma and Burkitt lymphoma)	231	25	11
ICD 84 (peripheral and cutaneous NHL)	33	2	6
ICD 85 (other and unspecified types of NHL)	52	3	6
ICD 88 (other malignant immunoproliferative diseases)	5	–	–
ICD 90 (multiple myeloma, plasmacytoma and malignant plasma cell neoplasms)	162	5	3

Table 4
MRI appearances of orbital/sinonasal lymphomas ($n = 24$).

Imaging features	Lesions, n(%)
T1 signal intensity	
Hypointense	6(25)
Isointense	17(71)
Hyperintense	1(4)
T2 signal intensity	
Hypointense	2(8)
Isointense	14(59)
Slightly hyperintense	8(33)
Enhancement intensity	
Marked	11(46)
Moderate	12(50)
Slight	1(4)
Enhancement homogeneity	
Homogenous	16(67)
Inhomogenous	8(33)

Table 5
Comparison of MR features between the diagnosed NHL.

MR features	PC	MALT	MC	DLC	MaC	P	BL	FC	UC	p values*
T2 signal intensity										$p = 0.65$
Hypointense				1		1				
Isointense	2	1	1	3	2	2	1	1	1	
Hyperintense		2	2	1	2	1				
T1 signal intensity										$p = 0.53$
Hypointense		1	1			1	1	1	1	
Isointense	2	2	2	5	4	2				
Hyperintense						1				
Enhancement intensity										$p = 0.2–1.0$
Slightly					1					
Moderate				5	2	2	1	1	1	
Marked	2	3	3		1					
Enhancement homogeneity										$p = 0.53$
Homogenous	2	2	2	2	2	3	1	1	1	
Inhomogenous		1	1	3	2	1				

PC, precursor cell NHL; MALT, mucosa associated lymphatic tissue NHL; MC, marginal cell NHL; DLC, diffuse large cell NHL; MaC, mantle cell NHL; P, plasmacytoma; BL, Burkitt lymphoma; FC, follicular cell lymphoma; UC, unspecified cell NHL.

* p-values were adjusted for multiple testing by using the Bonferroni correction.

4. Discussion

Primary extranodal lymphoma is defined as solitary extranodal site of a lymphoma with or without involvement of the contiguous lymph nodes at the time of diagnosis, or when the main bulk of the disease is located at an extranodal site [2]. The prevalence of orbital and sinonasal lymphomas is difficult to ascertain [2]. It varied from 1.5% to 8.0% in several studies [2–5]. Among 567 patients with different MID we could identify 36 cases with primarily orbital or sinonasal manifestation. In Western countries sinonasal lymphomas are very rare as we can confirm with our results. In Asia, however, they represent the second largest group of all extranodal lymphomas [3].

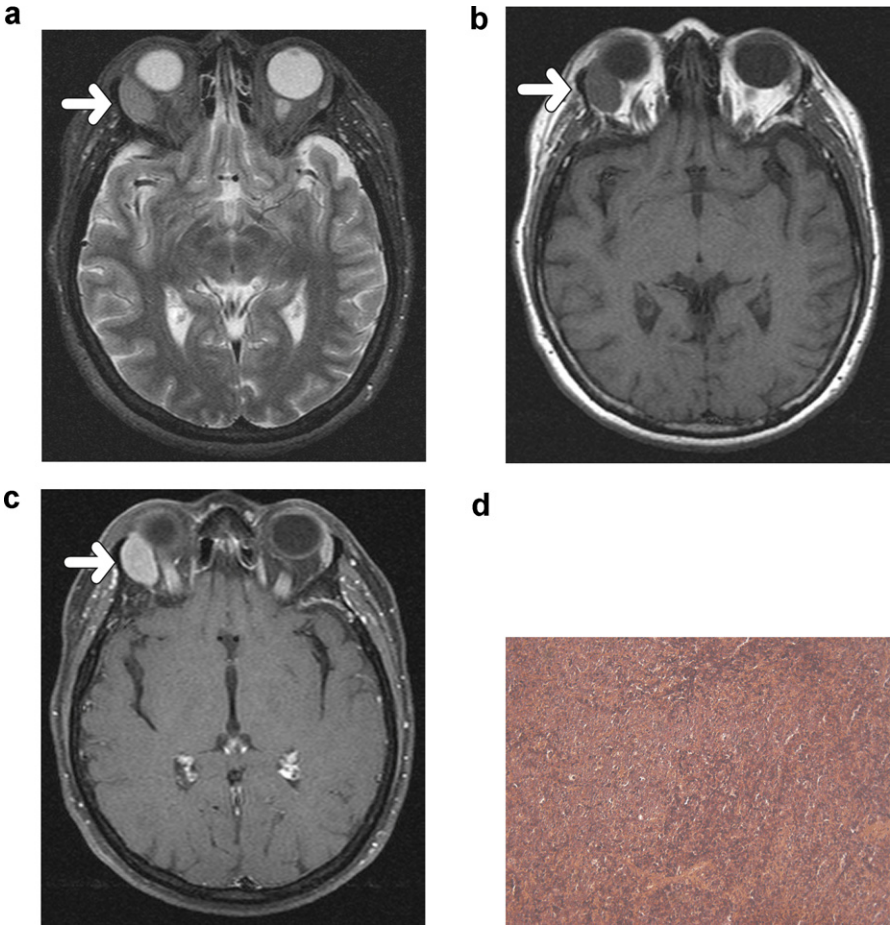

Fig. 1. 45-year-old man with diplopia and right-sided proptosis. (a) T2-w image with fat saturation shows an enlarged right lacrimal gland (arrow). The lesion is slightly hyperintense in comparison with the unaffected orbital musculature. (b) On T1-w image the lesion is isointense compared with the unaffected orbital musculature (arrow). (c) After contrast administration the tumour demonstrates the same enhancement as the unaffected orbital musculature (arrow). (d) Histology (hematoxilin & eosin stain, ×12.5) reveals a diffuse B-cell NHL.

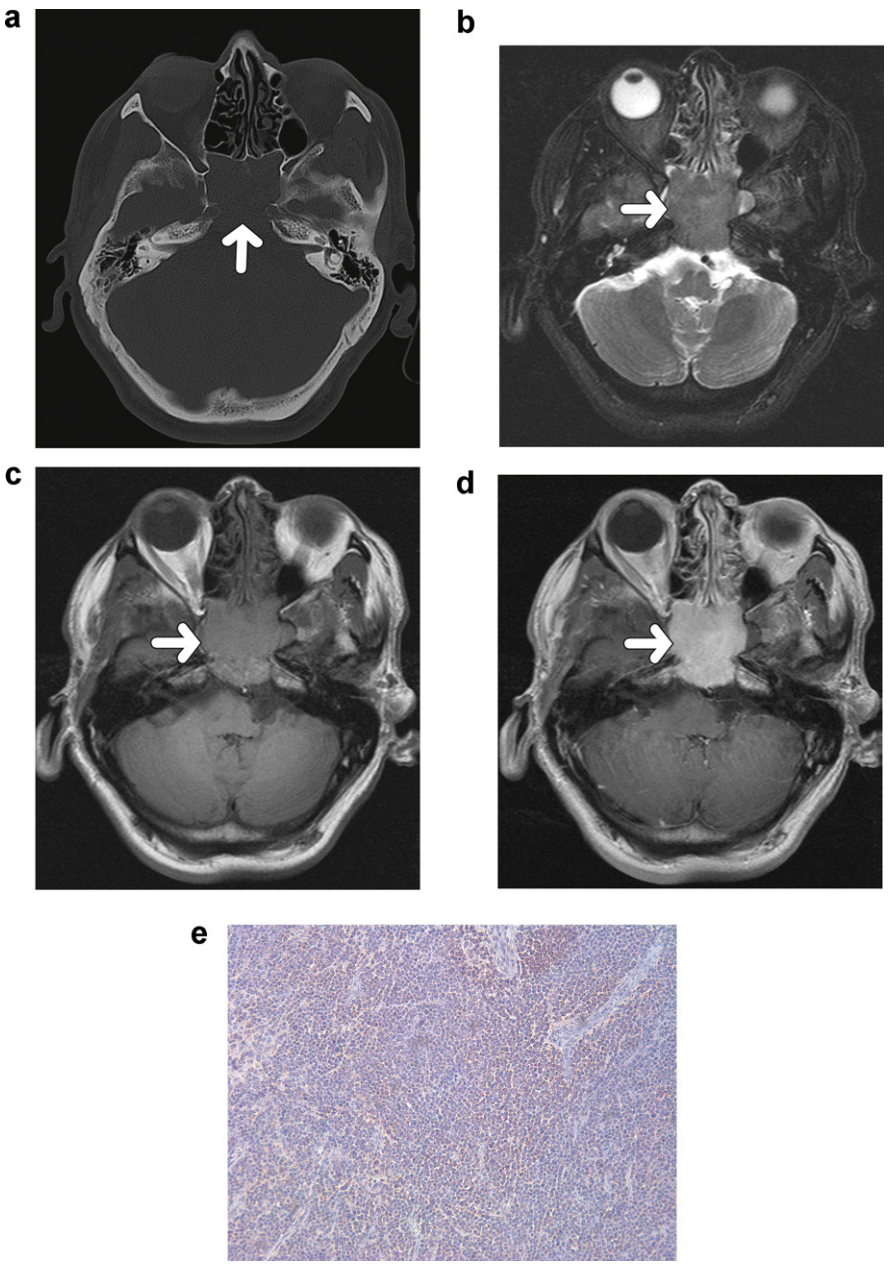

Fig. 2. 67-year-old patient with vision loss and diplopia. (a) CT with bone window setting documents destruction of the posterior wall of the sphenoid sinus (arrow). (b) On T2-w image with fat saturation the lesion (arrow) is isointense in comparison to the unaffected orbital musculature. The small hyperintense areas at the border correspond to inflammatory changes. (c) On T1-w image the lesion is isointense compared with the unaffected orbital musculature (arrow). (d) After administration of contrast medium the lesion shows a marked mainly homogenous enhancement (arrow) (e) Histology (hematoxilin & eosin stain, ×12.5) reveals a plasmacytoma (immunohistochemically strongly positive for light Kappa chains).

Symptoms are unspecific, caused by the mass effect, and depend on the site of the tumour in first line. A rapid development can be taken as hint of a malignant disease. As reported in the literature [3] most of our patients were older than 60 years. In these cases the age influenced the pre-therapeutic diagnosis. However, there were also one teenager and two children (precursor NHL).

Several subtypes of NHL may occur in the orbital and sinonasal region. As reported previously, in Asian countries most are T-/NK-cell lymphomas [2,3]. In Western countries B-cell lymphomas are the most common [2]. However, there are several reports that relativise this statement. Ferry and Harris as well as Abbondanzo and Wenig stated that most nasal lymphomas were T-cell NHL while most paranasal lymphomas originated from B-cells both in Western and in Asian countries [3,11]. It has been reported that diffuse large cell lymphomas should be the most frequent B-cell NHL of the orbital and sinonasal regions [2,3]. Other entities, such as follicular small cell lymphoma, MALT lymphoma, marginal cell lymphoma, Burkitt lymphoma, lymphocytic lymphoma, and anaplastic large cell lymphoma have been observed less often [3]. Rarely, extramedullary plasmacytoma and Hodgkin's lymphoma have been described [2,5,12]. In our analysis, diffuse NHL was identified in most cases. The percentage of extranodal plasmacytomas was relatively high with 14%. Compared to the subtypes described in the literature we found a frequency of sinonasal/orbital manifestation varying from 0% to 10% for the different NHL subtypes.

Radiologically, several features of orbital and sinonasal NHL have been described in the literature [7]. CT appearance should be nonspecific [6]. Sinonasal and orbital lymphomas often present as

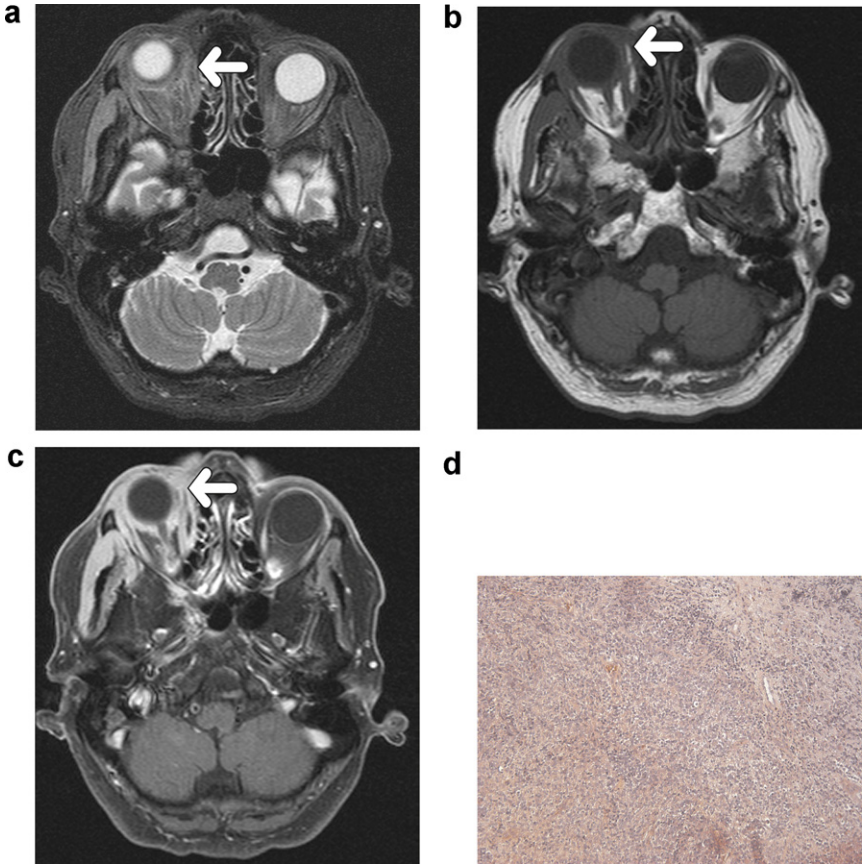

Fig. 3. 82-year-old patient with swelling of the right eye. (a) Periocular an inhomogenous, iso-/hypeintense, poorly demarked lesion is on T2-w image with fat at the right eye (arrow). (b) On T1-w image the lesion is isointense in comparison to the unaffected orbital musculature (arrow). (c) On contrast-enhanced fat saturated T1-w image the lesion shows a marked homogenous enhancement (arrow). Additionally, an infiltration of the right temporal muscle is seen. (d) Histology (hematoxilin & eosin stain, ×12.5) reveals a diffuse B-cell NHL.

masses of soft tissue attenuation [6–10]. Commonly, bone destruction and invasion of adjacent structures were found [6,7]. In the study of Nakamura et al. all patients with NHL of paranasal cavities and 54% of patients with nasal lymphomas had bone destruction [6]. As opposite to this Kim et al. found bony destruction only in 17% of their cases [7]. Some authors mentioned that several bony changes may occur in NHL like lytic or permeative bone destruction and bone remodelling [6–9].

In our analysis, on CT, masses of soft tissue attenuation with homogeneous moderate contrast enhancement were found in all instances. Bony destruction occurred in 31%, but only in patients with sinonasal lymphomas.

Previous studies on MRI features of sinonasal and orbital lymphomas comprised 8–16 patients [7,9–13]. According to the literature, most lymphomas of the orbital and sinonasal regions showed an intermediate signal intensity on T1-w images and were mildly to moderately hyperintense compared with the unaffected musculature on T2-w images without fat saturation [13]. However, hypointense signal on T2-w sequences has also been described previously [8]. After administration of contrast medium, moderate enhancement was reported in most of the cases [8–10].

Our study confirms the observation that lymphomas appear relatively dark on T2-w images. No case showed marked increased T2 signal intensity. In nearly all lesions T1 signal alterations were nonspecifically isointense in comparison to unaffected orbital or pterygoid musculature. After contrast administration marked or moderate homogenous enhancement was seen in most cases.

Kim et al. found a regional lymphadenopathy in 7% of the cases with sinonasal NHL [7]. In our study the percentage was higher (19%).

Several authors were concerned with criteria for the differentiation of malignant and benign lesions in the orbital and sinonasal regions [14,15]. According to Xian et al., most predictive MRI features for malignancy were an isointense signal on T2-w images, irregular shape of lesions, and ill defined margins [16]. However, aggressive inflammations may show similar changes [15]. Based on kinetic analysis it was postulated that malignant lesions typically show a wash-out type of time intensity curves [16]. In a later study, the same authors reported that cavernous hemangiomas, the most common orbital neoplasms in adults, showed a wash-out phenomenon on kinetic analysis in 39%, too [17].

According to the literature, other MR techniques, such as diffusion-weighted imaging (DWI) is helpful for the differentiation of malignant and benign lesions [18–20].

Authors who applied DWI observed lower ADC-values in malignancies in comparison to benign lesions [18–21]. Due to susceptibility artefacts DWI has limitations especially in the sinonasal region. Low ADC values of benign masses were reported in other regions [22]. In our patients DWI was not performed.

Bony destruction, invasion of adjacent structures, and perineural spread are signs of advanced malignancies [15], but may also occur in aggressive benign lesions. Akansel et al. reported that MR imaging alone may not allow a differentiation of malignant lymphoma from atypical lymphocytic infiltration [23]. Furthermore, T-/NK-cell NHL and some inflammatory diseases, such as Wegener's granulomatosis or invasive fungal sinusitis often show similar clinical signs and imaging features [9,15].

The differentiation between single malignant lesions in the orbital and sinonasal regions is also impossible because of similar

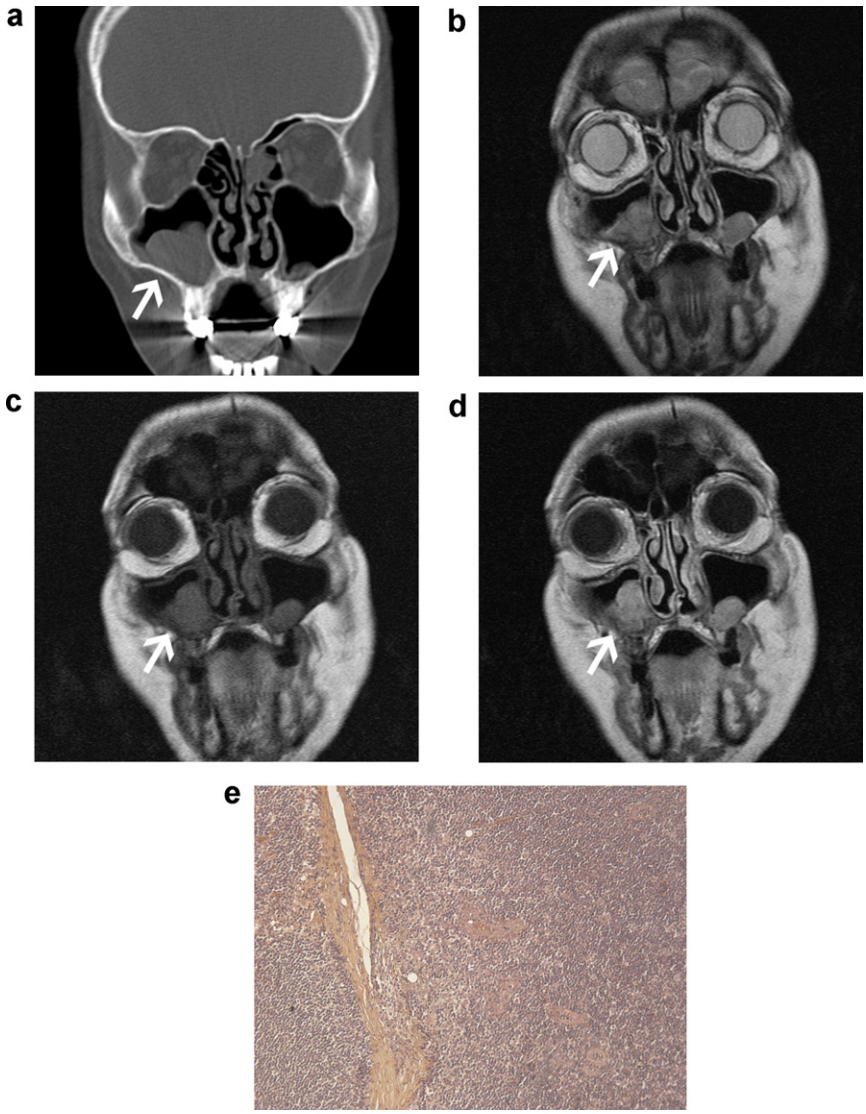

Fig. 4. 65-year-old patient with epistaxis. (a) CT with bone window setting documents a prominent polypoid swelling in the right maxillary sinus (arrow), a slight mucosal swelling in the left maxillary sinus and a partial opacification in the left ethmoid. There is no bony involvement. (b) On T2 w image the lesion is isointense in comparison to the unaffected orbital musculature (arrow). (b) On T1w SE image the mass is isointense (arrow). (c) Contrast-enhanced T1-w image shows a slight inhomogenous, moderate enhancement (arrow) which is not different to the contralateral side. (d) Histology (hematoxilin & eosin stain, ×12.5) reveals a plasmacytoma.

radiological patterns [14,15]. For example, most squamous cell carcinomas of the sinonasal cavity are hypointense on T2-w images similar to NHL [15]. Other malignancies, such as adenoid cystic carcinoma vary in their imaging features in accordance with tumour cell density and patterns [14,15]. Only if a sinonasal melanoma contains melanin a high signal intensity on T1-w images is suggestive for this type of neoplasm [14].

Although the combination of imaging sign together with a high age of the patient is sometimes helpful to make a correct suspected diagnosis, clear limitations for the prediction of dignity and type of neoplasms due to the overlap in the appearance on imaging have to be taken into account. Therapeutic planning requires not only a differentiation between a malignant and benign lesion or suggestion of the type of tumour, but the estimation of the exact histological subtype of the lymphoma. Imaging cannot deliver this information. Therefore, the diagnosis has to be made histopathologically.

Our analysis has several limitations. First, this is a retrospective study. Second, most patients underwent either only CT or MRI. Third, DWI and kinetic analysis after administration of contrast medium were not performed in our patients.

In conclusion, the frequency of primarily extranodal sinonasal/orbital lymphomas in our study was 6% with a varying percentage of subtypes between 0% and 11%. On CT lesions of soft tissue density with homogeneous slight to moderate contrast enhancement were found in all instances.

On MRI, most lesions were slightly hyperintense in T2w and homogeneously isointense in T1w in comparison to the orbital/pterygoid muscles and showed marked or moderate homogeneous enhancement after administration of contrast medium. There were no differences between imaging patterns in several NHL subtypes. The identified radiological features should be included in the differential analysis of lesions in the orbital and sinonasal regions, but they are not specific enough.

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