

# The Role of Fine Needle Aspiration of Orbital Lesions: A Case Series

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## Key Words

Clinicoradiological evaluation · Cytology · Fine needle aspiration · Orbital mass

## Abstract

**Objective:** This paper analyzes a series of ultrasound (US)-guided orbital fine needle aspirations (FNAs) which provide diagnostic information that cytopathologists approaching orbital lesions for the first time can find useful and underlines the importance of teamwork. **Study Design:** The investigators retrospectively obtained data from 24 consecutive orbital FNAs. For all patients, a complete clinicoradiological database was created. FNAs were performed under US guidance with 25-gauge needles and an aspiration biopsy syringe gun, and sent to the Department of Pathology for examination and data management. **Results:** The mean age of the patients was 54 years. Imaging studies included US, magnetic resonance imaging and computed tomography scans; 9 lesions involved the right orbit and 15 the left orbit. The mean lesion size was  $23.6 \pm 7.2$  mm. After microscopic examination, 7 smears were labeled as 'nondiagnostic', while in 17 cases a definitive diagnosis was proposed, which always proved to be correct (70.8%, specificity = 100%). **Conclusions:** The investigators believe that FNA biopsy of or-

bita masses is a necessary step; its weaknesses lie in the particularly delicate site of sampling and the extreme heterogeneity of lesions. Nevertheless, when orbital FNA is performed within a well-coordinated multidisciplinary team, it is a powerful tool that can be used to define the most appropriate management of these patients.

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## Introduction

Given the complex nature of its anatomical structure, the orbital cavity can host an extremely diverse array of mass-forming lesions, with each of them requiring different therapeutic approaches, ranging from simple follow-up and/or medical therapy to more aggressive surgical management. The relative frequency of single lesions varies greatly in the literature, but there is general consensus regarding which entities are the most frequent; one of the largest studies available reports a frequency of 17% for vascular tumors and 11% for inflammatory, lymphoid lesions and secondary lesions, followed by ocular adnexal tumors, neurogenic tumors and cysts [1]. Moreover, the periocular area is a particularly delicate region, thus invasive diagnostic techniques are to be used sparingly in or-

der to keep the risk of complications as low as possible. In the majority of cases, a tissue sample is often required and fine-needle aspiration (FNA) biopsy has been extensively used and studied since the 1970s [2]. Preoperative clinical and radiological findings, although essential, are not completely capable of providing a conclusive diagnosis for etiological definition and therapeutic purposes. The diagnostic, and sometimes therapeutic, path of the patient with an orbital mass can end with FNA, or, alternatively, it can provide the surgeon with the information needed to decide and guide treatment of the mass. This paper analyzes a series of ultrasound (US)-guided orbital FNAs, which provide diagnostic information that cytopathologists approaching orbital lesions for the first time can find useful and underlines the importance of teamwork between clinicians and radiologists for the management of this particular anatomical localization of pathology.

## Materials and Methods

We retrospectively collected data regarding 24 consecutive patients (14 females and 10 males) who were admitted to the Department of Maxillofacial Surgery, San Gerardo Hospital, Monza, Italy, following clinical evidence of orbital swelling and subsequently underwent FNA for diagnostic purposes. The mean age of the patients was 54 years, ranging from 14 to 87. For all the patients included in the study, a complete clinicopathological database consisted of: (1) results of the physical examination, (2) US findings, (3) computed tomography (CT)/magnetic resonance imaging (MRI) features and (4) FNA report. FNAs were performed under US guidance with 25-gauge needles and an aspiration biopsy syringe gun by a team of expert pathologists and radiologists at the Department of Interventional Radiology (San Gerardo Hospital). Two to four smears per patient were performed. Conventional smears were stained with Papanicolaou or May-Grünwald-Giemsa; a Diff-Quick on-site evaluation was always performed in order to evaluate the adequacy of the sample. The practical consequences of the combined clinical, radiological and pathological reports were divided into: (1) invasive diagnostic surgical biopsy, (2) surgical excision of the lesion or (3) medical treatment/follow-up (fig. 1a, b). The choice of the surgical approach to the tumor was made according to the position and the suspected diagnosis, and the pros and cons of performing a single incisional biopsy or a resection were evaluated. Different techniques were used, including coronal and semicoronal, transpalpebral and transconjunctival approaches. In order to approach bulky tumors and tumors located in deep spaces, a bone orbitotomy with subsequent repositioning and osteosynthesis of the bony segments was performed. In surgically treated patients, a cytohistological correlation was available and surgical specimens were sent to the Department of Pathology (San Gerardo Hospital) for examination. Data management was performed using MS Office Excel 2007. The study was performed according to the rules stated in the Declaration of Helsinki and was approved by the Institutional Review Board; due to its retrospective observational nature, informed consent was not needed.

**Table 1.** Correlation between the definitive diagnosis and FNA outcome

Definitive diagnosis (n = 24)	Total	FNA result
Inflammatory process	7	x x x x x ○ ○
Benign cyst	6	x x x x x x
Pleomorphic adenoma	2	x x
Extranodal marginal zone B lymphoma	2	○ ○
Cavernous hemangioma	2	○ ○
Epithelioid hemangioendothelioma	1	○
DLBC	1	x
Plasmacytoma	1	x
Melanoma	1	x
Metastasis (RCC)	1	x

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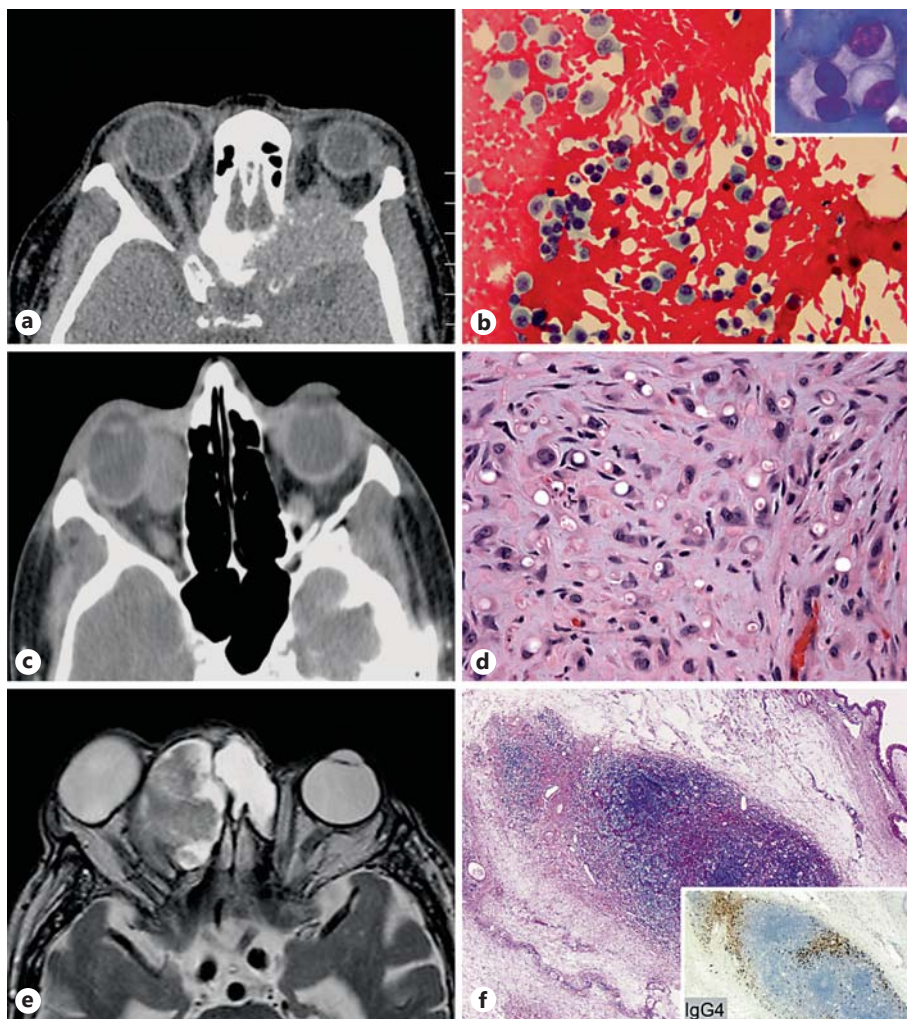
x = Diagnostic smear with correct cytohistological correlation; ○ = non-diagnostic smear.

**Table 2.** Correlation between FNA category and patient management

FNA category	Excision	Surgical biopsy	Follow-up	Total
Nondiagnostic	3	4		7
Benign				
Cysts	2		4	6
Inflammation		1	4	5
Tumors	2			2
Malignant tumors	1	1	2	4

## Results

The great majority of patients came to the clinician's attention due to mass-related symptoms; only one lesion was found incidentally during a CT scan performed for other purposes. The most common symptoms were diplopia (56%), proptosis (30%) and pain (10%), while there were rarely alterations in lacrimation (4%). An US scan was performed on all patients while 8 were subjected to MRI and 11 to CT as a second-level imaging study (2 of the patients included in the second-level study underwent both a CT and MRI scan). Lesions were always unilateral: 9 were involved in the right orbit and 15 in the left. At US examination, the lesions ranged from 15 to 37 mm in diameter (mean  $23.6 \pm 7.2$ ). Two patients suffered from a slight postprocedural soft tissue hemorrhage. After microscopic examination, 7 cytological smears were labeled as 'nondiagnostic', while in 17 cases a definitive diagnosis was proposed (table 1). In table 2, a comparison between



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**Fig. 1.** CT scan (a) showing extensive destruction of the left orbit walls by a low-density mass; its smear (b) was heavily hemorrhagic but contained also numerous atypical plasma cells, leading to the diagnosis of a localized plasmacytoma. c CT scan of another patient shows a better-defined low-density mass in the right orbit dislocating the eye bulb; smears yielded only blood cells. Upon surgical excision (d), it was diagnosed as epithelioid hemangioendothelioma. e MRI of a patient with a right orbital mass which was diagnosed as pseudolymphoma (f). Pseudolymphomas are defined as a benign lymphoid hyperplasia with marked lymphocyte and plasma cell infiltration and fibrosis.

the cytological diagnoses and follow-up results is shown. In our case series, there were no false-positive or -negative results: when the lesion was correctly sampled and smeared, a correct definitive diagnosis was always obtained (in 17 of 24 cases, 70.8% with a specificity of 100%).

#### *Nondiagnostic FNAs*

Of 7 nondiagnostic FNAs, 2 were performed in less-defined lesions with irregular borders and inconclusive radiological features. Due to the ambiguous clinicopathological triage, patients underwent an incisional diagnostic procedure that confirmed a final diagnosis of orbital pseudotumor, which is defined as an idiopathic tumorous inflammation made up of a pleomorphic inflammatory cellular response and a fibrovascular tissue reaction. Clinically, orbital pseudotumors were categorized as either myositis or dacryoadenitis. A further 3 of the 7 nondiag-

nostic smears came from hemorrhagic FNAs with radiological appearances suspicious for vascular tumors, and complete surgical excision revealed 2 cavernous hemangiomas and 1 epithelioid hemangioendothelioma (fig. 1c, d). Only 2 cases represented truly inadequate samples and were represented by acellular smears in patients with radiological lesions suspicious of lymphoproliferative processes. Final histology, obtained by surgical incisional biopsy (one using a transpalpebral and the other a transconjunctival approach), revealed two extranodal marginal zone B-cell lymphomas.

#### *Benign Entities: Cysts, Tumors and Inflammatory Lesions*

Cytological evaluation led to a final report of benign in 13 cases, with cysts being the most frequent entity (n = 6; 4 mucoceles, 1 keratinic cyst and 1 lymphangioma). In 4

of these cases, FNA also represented a therapeutic procedure, being performed as a decompressive evacuation. Smears from the content of mucoceles included mucinous material, inflammatory cells and rarely respiratory epithelium. Smears from keratinic cysts yielded anuclear squamulae while lymphangiomas showed chylous fluid with faint lipid vacuolation due to the high triglyceride content.

Following US-FNA revealing a lymphocyte-rich background, a large nodule in the lateral wall of the orbital region underwent surgical biopsy and was assigned a final diagnosis of pseudolymphoma (fig. 1e, f).

Four of the smears were labeled as 'inflammatory' and, being supported by a benign radiological appearance or clinical history of orbital cellulitis, the decision of a conservative management (clinical follow-up) was made. These smears can show complete absence of epithelial or atypical cells with an extreme variability in the classes of phlogistic cells and amount of necrosis, thus being non-diagnostic from the pathological point of view. However, they can still provide information that is of importance to clinicians when attempting to make the correct diagnostic decision.

Two benign tumors of the lacrimal gland were found (pleomorphic adenomas) that subsequently underwent complete surgical excision using a hemicoronal approach associated with lateral and superior orbital rim orbitotomy. Ocular pleomorphic adenoma is characterized by single, or clusters of, cells that are uniform in size. These cells are associated with a moderate amount of well-defined cytoplasm and round-to-oval eccentric nuclei that contain evenly distributed granular chromatin immersed in the typical metachromatic matrix and are visible using the May-Grünwald-Giemsa stain (fig. 2a-c).

### *Malignant Entities*

Cytological analysis led to a final diagnosis of malignancies in 4 cases: 1 diffuse large B-cell lymphoma (DLBCL), 1 plasmacytoma, 1 melanoma and 1 metastasis from renal cell carcinoma (RCC). In all these cases, immunocytochemistry on routine smears or cell blocks was performed in order to confirm the diagnosis. The DLBCL diagnosis was verified by performing an immunohistochemical study on an incisional transconjunctival biopsy; the following chemotherapy led to complete disease remission (fig. 2d-f).

In plasmacytoma, FNA showed numerous, atypical plasma cells accompanied by extensive hemorrhaging. In metastatic RCC, orbital smears were characterized by the presence of atypical epithelial cells, cells with enlarged

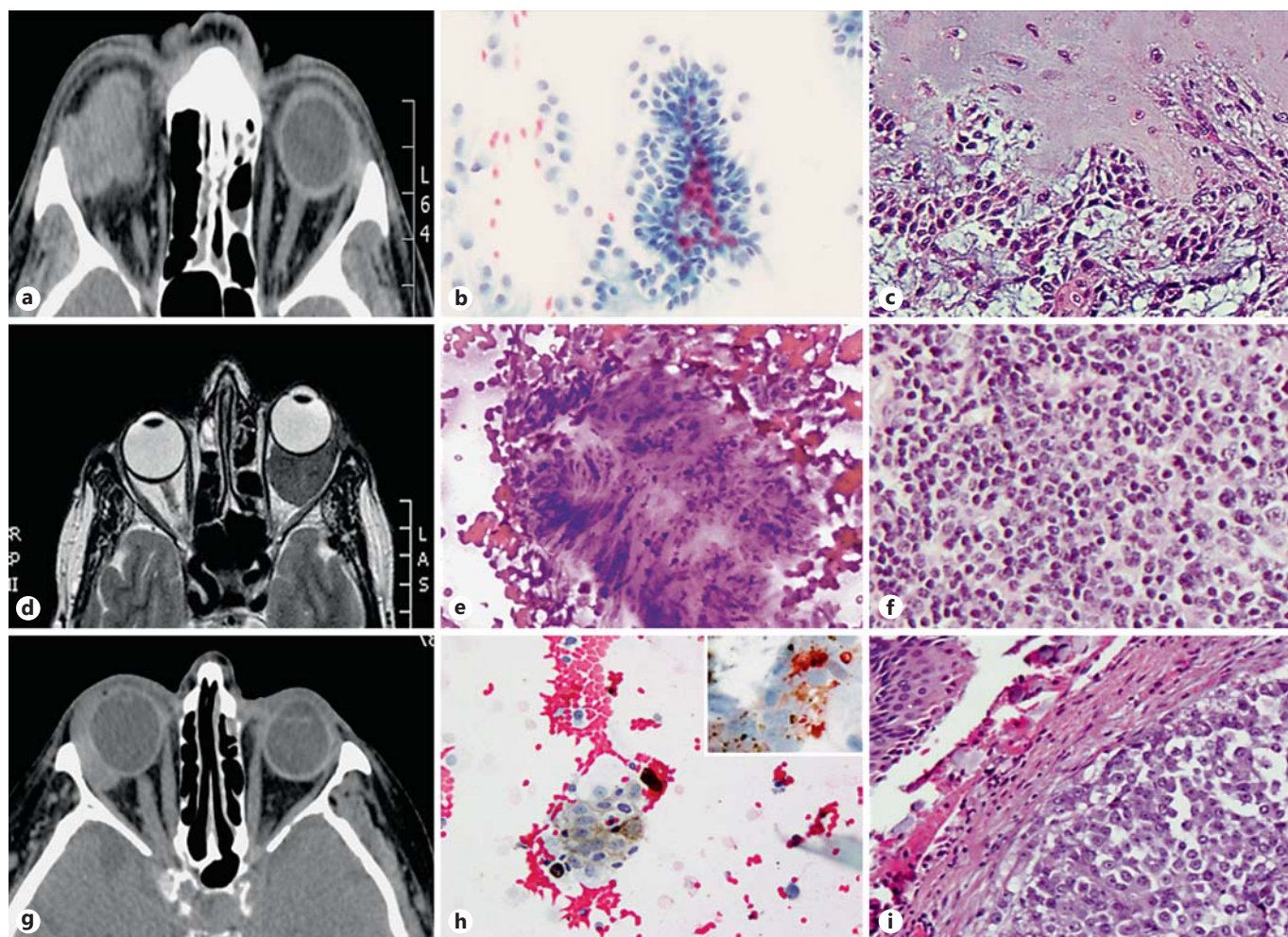
nuclei with prominent nucleoli and a moderate-to-abundant amount of granular cytoplasm (fig. 1a, b).

The cases of plasmacytoma and metastasis from RCC did not require histological confirmation; prognosis for these patients was poor as they showed multiple systemic lesions and were treated with medial palliative therapy protocols. Cytological smears from melanoma consisted of atypical epithelioid cells (single and in clusters) with focal brown pigmentation; positivity for melan-A immunocytostain confirmed the diagnosis of choroidal melanoma (fig. 2g-i). A debulking procedure, which required orbital exenteration with temporalis muscle flap reconstruction and neck dissection for multiple metastatic nodes, was planned. The patient died a few months later as a result of cranial base recurrence and lung metastases.

### **Discussion**

Due to the rarity and variability in pathological entities that can arise in the orbital cavity, this field of pathology is one that lacks standardized patient management, and each case must be thoroughly studied in order to determine the best approach. The most important clinical variables are the age of the patient and medical history [3], which can either suggest or exclude certain diagnoses (for example, cystic lymphangiomas are more likely to manifest themselves at a young age; more patients with orbital pseudotumors may have swollen eyelids, conjunctival congestion, pain, retinal folds or hemorrhage and optic nerve atrophy than patients with lymphoid tumors [4]). The first diagnostic step after clinical examination is represented by imaging techniques. US, CT and MRI are often used in the aforementioned sequence to further characterize the lesions [5]. In CT and MRI studies, inflammatory processes may present with diffuse orbital masses, uveoscleral thickening, contrast enhancement of Tenon's capsule, proptosis and optic nerve and extraocular muscle enlargement. On the contrary, tumors show well-defined nodular-like appearances, with the possible existence of malignant features such as necrosis, soft-tissue infiltration or bone lytic lesions. As for other solid masses, they often give off low-density (or low-intensity) signals, but are otherwise less characteristic lesions.

Upon MRI, areas of inflammation or enhancing tissue can be masked by the high signal intensity of orbital fat and involvement of the fat itself may not be appreciated. Imaging features of patients with orbital pseudotumors have been studied by MRI using frequency-selective fat saturation and Gd-DTPA [4]. On the other hand, for cys-



**Fig. 2.** CT scan (a) of a pleomorphic adenoma in a patient admitted for painful diplopia of the right eye; a smear (b) and final histological correlation (c) show the typical features of pleomorphic adenoma. d-f Case of a patient with a deep mass in the left eye socket (d; MRI scan) which yielded scarce, artifactual cells (e) that, given also the radiological suspicion, were deemed suggestive of a

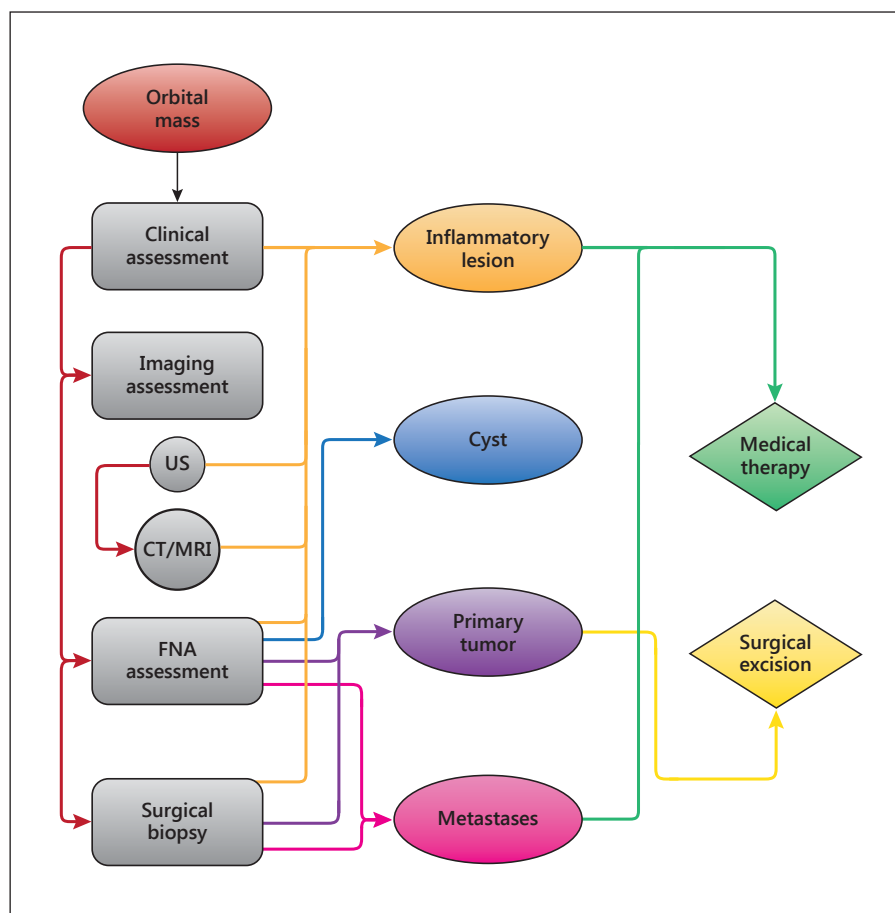
nerve sheath tumor. However, surgical biopsy revealed an extranodal marginal zone lymphoma (f). g-i A patient with an infiltrating lesion of the right eye (g) whose smear showed atypical pigmented epithelioid cells positive for Melan-A (h) was diagnosed with choroidal melanoma and subjected to orbital exenteration (i).

tic lesions, imaging analysis is often helpful and, after FNA, a conservative approach can be easily managed. In many circumstances, clinicopathological correlations are a fundamental step, and orbital biopsy is required to solve the differential diagnosis and to make a therapeutic decision (a putative flowchart is proposed in fig. 3).

Both cytological and histological sampling are viable options, but the former is preferred due to its low invasiveness and its near absence of complications and dissemination (a particularly dreaded eventuality for epithelial tumors such as pleomorphic adenoma). However, FNA smears are burdened by some disadvantages, such

as samples being classed more prevalently as 'nondiagnostic'; due to a lack of material, the use of immunostains is often impossible and ultimately leads to a higher risk that a lesion cannot be characterized. Lesion size, a common issue throughout all types of anatomical sites studied with cytology (i.e. thyroid [6] or lung nodules [7]), is surprisingly not a limiting factor of FNA performance, as our nondiagnostic rate also increased for smaller targets, especially those <20 mm in maximum diameter. Another variable that can affect the performance is the exact site of the radiological target, which can be superficial (lacrimal glands, tear ducts or eyelid) or deep into the orbital

**Fig. 3.** Decisional algorithm in the evaluation of orbital masses is proposed. Red arrows (see online version for colors) on the left side of the picture indicate a nonconclusive/dubious outcome of the different assessment steps; otherwise, colored arrows on the right side indicate that a definitive diagnosis and an operative decision have been established. The first step should always be a thorough clinical examination, which can often be the only one required in the case of obvious acute inflammation. As a second-level test, imaging studies should be performed (firstly US and then possibly CT/MRI), which can confirm the clinical suspicion or require additional steps, such as orbital FNA. This procedure is usually able to establish the operative indication for the patient in case of inflammatory lesions, and primary and secondary tumors or cysts, for which FNA can also be a therapeutic option. Otherwise, a surgical biopsy acts as the final diagnostic step.



cavity, a location that can result in dislocation of the eye bulb. It is up to the skills of the cytopathologist, aided by data and advice provided by clinicians and radiologists, to manage the precious material in the best of ways and come to a conclusion based upon the cytological features of each sample.

#### *Benign Cysts*

Cysts (reported frequency: 6% [1]) are typically represented by keratinic [8], mucous and lymphangiomatous [9] variants; the specific subtype can be noted by analyzing the characteristics of the epithelial layer or its amorphous content. Keratinic cysts can appear at all ages, but their localization is often superficial (eye lid) and they can present as small discontinuities in the orbital wall in imaging tests performed for dubious cases. In differential diagnosis, malignant entities (squamous cell carcinoma) are almost invariably and easily ruled out. In patients with a medical history of recurrent sinusitis, mucoceles can more often lead to clinical and radiological suspicion of

malignancy due to the more striking symptoms (pain, swelling and dislocation of the eye bulb) and the mildly erosive behavior towards the skull. Lymphangiomas are associated with younger age groups and are thin-walled cysts that can reach many centimeters in diameter. In these cases, FNA can also represent a therapeutic intervention by aspiration and can therefore promote a reduction in the compressive symptomatology of the cyst (in our institution, these lesion types were always sampled by applying suction using a 20-ml syringe).

#### *Vascular Tumors*

These lesions are a real challenge for the orbital multidisciplinary team, as not even cytological smears can discern between benign and malignant entities in cases of localized disease given that they consist entirely of hemorrhagic material. For hemangiomas (reported frequency: 9% [1]), differential diagnoses following imaging techniques include, in all age groups, schwannoma, optic nerve sheath meningioma, lymphoma and pseudotu-

mors, while rhabdomyosarcoma, fibromatosis and fibrosarcoma should be taken into consideration for pediatric patients. In our case series, epithelioid hemangioendothelioma had the same cytological appearance (fig. 1c, d). The observation of a completely hemorrhagic FNA can provide important information to the surgeons in order to exclude the spectrum of entities previously cited and thus lead to a histological sampling for the correct diagnosis (100% in our case series).

### *Inflammatory Lesions*

First described by Birch-Hirschfeld in 1905, the 'idiopathic orbital inflammatory syndrome', also known as an orbital pseudotumor, is a nonspecific, nonneoplastic inflammatory process of the orbit [4]. Orbital inflammation, particularly the fibrotic form, can represent a distinct disease entity that may require aggressive intervention. However, in general, if the clinicopathological correlation suggests the possibility of a localized or more diffuse inflammatory process to the orbital cone, treatment options are conservative follow-up and medical therapy. The ocular manifestations of orbital pseudotumors may include periorbital edema, erythema, proptosis, ptosis, diplopia and pain with eye movements. FNAs can show a complete absence of epithelial cells with variability in the amount of neutrophils, and lymphoid and plasma cells depending upon the etiological nature of the process. The final cytological report can often be nondiagnostic from the pathological point of view, but informative for clinical decision making. Exceptional tumor-like appearance can be related with pseudolymphomas. Recent data suggest that a significant part of benign lymphoid hyperplasia can be associated with IgG4-related orbital disease using the comprehensive diagnostic criteria for IgG4-related disease [10].

Lesions of lacrimal glands and tear ducts [11, 12] can often lead to alarming signs and symptoms, such as mass formation and dislocation of the eye globe, and need, therefore, to be investigated further by cytological smears [13].

Pleomorphic adenomas account for up to 8 of 29 cases of benign orbital tumors in recent studies [2]. Fortunately, these types of tumors have extremely typical cytological features and can be diagnosed with such a low-impact technique, for they tend to spread locally rather easily, with serious consequences on the prognostic outlook. For these reasons, and given the anatomic peculiarity of the periocular region, surgical approaches to these tumors are always destructive.

The observation of necrosis and large polygonal cells arranged either singly or in rosettes, clusters or sheets can

suggest a degeneration in carcinoma ex adenoma [11]. Other examples are mucoepidermoid carcinoma [14], which shows both mucous and squamous keratinizing malignant elements in smears, and adenoid cystic carcinoma, which is fairly difficult to characterize with FNA other than establishing its nature as an epithelial malignant tumor [12].

### *Lymphomas*

The orbit represents a popular site for lymphomas [15] (around 10% [1] of orbital masses), both low-grade (mainly extranodal marginal zone B-cell lymphoma and follicular lymphoma) and high-grade forms (DLBCL [16] and Burkitt's lymphoma [17]). Tumors of the T lineage are very rare and are mainly represented by the involvement of the eye socket by an extranodal nasal type [18] NK/T-cell lymphoma. In our case series, lymphomas presented themselves as slow-growing, low-density masses causing diplopia and pain. This led to a differential diagnosis with many other entities, both benign and malignant (mucocele, vascular masses and pseudolymphomas). FNA material is seldom adequate for a complete characterization of the lesion, but it can help as a first triage, guiding the surgeons who will perform incisional biopsy and enabling them to choose the most correct surgical approach [19, 20]. Cytological criteria rely mainly on the report of a monomorphic population of lymphoid cells without benign features (i.e. tingible body macrophages) [21] for low-grade lymphomas, but only when the FNA yields sufficient material. In deep-localized tumors, such as lymphomas, FNAs can show hypocellular samples despite the use of an aspiration gun. Moreover, lymphoid lesions are often accompanied by extensive sclerosis and this can be another cause of inadequate smears with a high degree of artifacts, as was the case with the 2 extranodal B marginal zone B-cell lymphomas in our case series. For the DLBCL present in our case series, however, large, atypical lymphoid cells led the cytopathologist to formulate a diagnosis of malignancy (fig. 2d-f).

### *Metastases and Rare Malignancies*

Within a strong clinical setting, FNA alone can represent the only and conclusive intervention required. Furthermore, in these not uncommon cases (relative frequency: 11% [1]), it also serves as a confirmation of the diagnosis [22, 23], as demonstrated by our plasmacytoma (fig. 1a, b) and RCC-affected patients [24].

There are also highly malignant tumors [25, 26] for which the eye is one of the most frequent localization, such as melanoma (fig. 2g-i; reported frequency 3% [1]).

## Conclusions

In conclusion, we believe that FNA biopsies of orbital masses are a necessary step. Its weaknesses lie in the particularly delicate site of sampling (eye globe and surrounding structures) and the extreme heterogeneity of

lesions, which can frequently make clinicoradiological evaluation before FNA quite difficult. Nevertheless, within a well-coordinated multidisciplinary team, orbital FNA is a powerful tool that helps to define the correct management of these patients. A flowchart for the management of orbital masses is proposed in figure 3.

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