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Orbital Muscle Enlargement: What if It's Not Graves' Disease?

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Abstract
Purpose of Review To provide the radiologist with tools to recognize findings atypical for Graves' ophthalmopathy and differentiate between the most important and common alternative causes of extraocular muscle enlargement on CT and MR imaging.
Recent findings We introduce five 'red flags' representing features that are atypical for Graves' ophthalmopathy: unilateral disease, atypical pattern of muscle involvement, adjacent structure involvement, restricted diffusion, and absence of pain.
Summary About 95% of the cases with extraocular enlargement are due to Graves' ophthalmopathy, other causes are less well known and recognized. The 'red flags' may aid in recognizing and suggesting alternative diagnoses.

Keywords Extraocular muscle enlargement · Graves' ophthalmopathy · Atypical causes · Overview

Introduction

The most known and common cause of orbital muscle enlargement is Graves' ophthalmopathy (GO). This is an extra-thyroidal manifestation of Graves' disease and occurs in about 25–50% of the patients with Graves' disease [1]. The prevalence is higher in women, but the disease tends to be worse for men [2, 3]. GO is defined as an autoimmune inflammation of the orbital and retro-orbital soft tissues. The most characteristic signs of GO are swelling of the extraocular muscles and orbital fat [4]. However, when encountering a patient with extraocular muscle enlargement, other etiologies should also be considered. Lacey et al. described 1849 cases with extraocular muscle enlargement of which 95% were due to GO and 5% were due to other causes [5, 6•].

Most radiologists know how to report a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the orbit with GO, but it becomes more challenging when alternative causes of extraocular muscle enlargement are present. The first step is recognizing when the imaging does not meet the requirements or is at least atypical for GO. This is very important since the radiologist can be the first to suggest a different diagnosis. Second, an alternative diagnosis or differential diagnosis should be found. This article will elucidate characteristics that are atypical for GO: the 'red flags'. We will illustrate the most important and most common alternative causes of extraocular muscle enlargement that may be suggested based on the 'red flags'.

Graves' Orbitopathy

Patients with GO can present with pain, proptosis, eyelid retraction, inflammation of the eyelids and conjunctiva, restricted ocular movement, diplopia, optic neuropathy and vision loss [7•]. The eye disease is bilateral in most cases, but in 10% of the patients it is unilateral [2]. Age of onset is usually around 40 to 60 [4]. Not all patients with Graves' disease develop GO.

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The main purpose of imaging in patients with GO is to confirm the clinical diagnosis or assess treatment response. Patients without clinical signs of orbitopathy may have enlargement of the extraocular muscles on imaging [3]. Besides, patients with unilateral clinical disease may show bilateral involvement on imaging [2].

CT and MRI are both appropriate for the assessment of extraocular muscle size. The advantage of MRI is extra information about the state of the muscles. Two different phases of clinical disease can be distinguished: (1) the 'active phase' with inflammation and edema of the extraocular muscles, lacrimal gland and adipose tissue (2) the 'inactive or chronic phase' with fibrosis and fatty infiltration of the extraocular muscles [8]. In both stages there may be enlargement of the extraocular muscles, but in the 'active phase' MRI shows T2 hyperintense extraocular muscles in addition (Fig. 1). Fatty degeneration in the 'chronic phase' is best observed on non-fat saturated T1-weighted images [9]. The differentiation between these two phases can be important for GO treatment: immunosuppressive therapy or radiotherapy may work in the 'active phase' but not in the fibrotic stage [8]. The role of contrast enhancement in these phases is not quite clear: some studies show decreased contrast enhancement in the 'active phase' owing to destruction of the microcirculation, other studies show increased contrast enhancement in the 'active phase' due to vascular congestion [8].

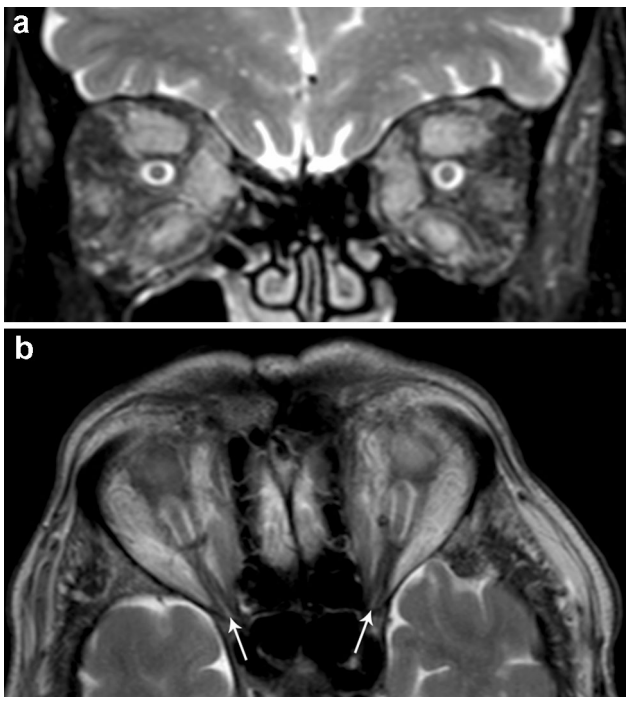

Fig. 1 Graves' orbitopathy. **a** Coronal fat-suppressed T2-weighted image shows bilateral enlargement and edema of the inferior rectus, medial rectus, and superior rectus muscle. **b** Axial T2-weighted image with stretching of the optic nerve with less cerebrospinal fluid around the nerve (arrows)

Involvement of the extraocular muscles in GO has a typical pattern: the inferior rectus muscle is most frequently affected, followed by the medial rectus, superior rectus (with the levator palpebrae), lateral rectus and oblique muscles, also memorized as the mnemonic 'I'M SLOw' [10]. The belly of the muscle is enlarged and the tendinous insertion is typically spared. The coronal plane can best be used for evaluation of the extraocular muscles or possible optic nerve compression.

Red Flags

In this chapter we list characteristics that should prompt radiologists to consider alternative causes of extraocular muscle enlargement. These red flags and possible differential diagnosis are summarized in Table 1.

Unilateral

Extraocular muscle enlargement is bilateral in 90% of the GO cases [2]. Unilateral may still represent GO when following the typical pattern of muscle involvement, but other possible diagnoses should at least be considered. These are lymphoma, idiopathic orbital inflammation (IOI), cellulitis, metastasis and vascular etiologies.

Atypical Muscle Involvement

The extraocular muscles involvement in GO follows the I'M SLOw mnemonic: inferior rectus, medial rectus, superior rectus (with the levator palpebrae), lateral rectus and oblique muscles. When there is a single muscle enlarged other than the inferior rectus or muscle involvement occurs in a different pattern, alternative causes should be considered.

IgG4- related ophthalmic disease (IgG4-ROD), lymphoma, metastasis and sarcoidosis have a predilection for the lateral rectus muscle. In IgG4-ROD multiple muscles may be involved, but overall the lateral rectus muscle is most frequently affected and the inferior rectus and medial rectus are usually spared [11–13]. Metastasis can occur in any extraocular muscle but has a preference for the lateral rectus muscle.

The superior rectus muscle is the most affected muscle in lymphoma and sarcoidosis [14, 15]. In both diseases the superior-lateral quadrant is most frequently affected with enlargement of the superior and lateral rectus muscles.

The medial rectus muscle is the most common affected muscle in orbital cellulitis as this muscle has a close relation with the ethmoidal sinus [2, 14]. IOI also has a preference for the medial rectus muscle, but involvement of the other rectus muscles is also possible [16, 17].

Table 1 Red flags with possible differential diagnosis

Red flag	Possible differential diagnosis
Unilateral	Lymphoma
	IOI
	Orbital cellulitis
	Metastasis
	Vascular etiologies
Atypical muscle involvement	
Lateral rectus predilection	IgG4-ROD
	Lymphoma
	Metastasis
	Sarcoidosis
Superior rectus predilection	Lymphoma
	Sarcoidosis
Medial rectus predilection	Orbital cellulitis
	IOI
Involvement of adjacent structures	
Cavernous sinus / orbital fissure	Orbital cellulitis
	IOI
Salivary glands	IgG4-ROD
	Sarcoidosis
Restricted diffusion	Lymphoma
	Metastasis
Absence of pain	Lymphoma
	IgG4-ROD

Involvement of Adjacent Structures

In GO the lacrimal gland might increase in size and show hyperintensity on T2 due to inflammatory edema [18]. Although it is seen in GO, other diagnoses as: lymphoma, IOI, IgG4-ROD, cellulitis, sarcoidosis and GPA are more likely [19•].

When the cavernous sinus or orbital fissure are involved, orbital cellulitis and IOI are to be considered.

The salivary glands may be affected in IgG4-ROD and sarcoidosis.

Restricted Diffusion

Restricted diffusion should not be encountered in GO. The presence of restricted diffusion in enlarged extraocular muscles raises the suspicion of a malignancy such as lymphoma or metastasis.

Clinical Sign: Absence of Pain

There is a lot of variation in the clinical presentation of a patient with enlarged extraocular muscles. As GO regularly presents with pain, the complete absence of pain is somewhat atypical. Overall, when there is no pain and the presentation is not acute, a neoplastic cause should be considered [5]. Typical painless causes of muscle enlargement are lymphoma and IgG4-ROD.

Alternative Causes of Extraocular Muscle Enlargement

Lymphoma

This is the most common primary orbital malignancy in adults and accounts for about 55% of the orbital neoplasms [20, 21]. The most common described cases of orbital lymphoma are of B-cell origin of which the most frequent type is extranodal marginal zone B-cell lymphoma [22, 23]. The conjunctiva, eyelid, orbital connective tissue and lacrimal gland are most frequently involved [23]. Primary extraocular muscle lymphomas are rare, it accounts for about 0.1% and 8.7% of all extranodal lymphomas [24, 25]. In most cases extraocular muscle involvement is due to infiltration of extramuscular masses [26, 27].

Unilateral thickening of the muscle and tendon is most common [24]. The cases that are bilateral (about 25%) are usually high grade lesions [21]. The most typical location of involvement is the superior-lateral quadrant [28]. The rectus muscles are more frequently affected, especially the superior rectus and lateral rectus muscles, but the lacrimal gland and eyelid in this quadrant may also be infiltrated [14, 25, 28]. Advanced cases can show sinus bone erosion and intracranial spreading. Due to mass effect patients experience proptosis, diplopia and motility disturbances, similar to symptoms in GO [21]. Sometimes there is ptosis and a palpable mass. A key clinical feature is that patients usually experience no pain [29].

CT typically shows a hyperdense, enhancing mass with or without the lacrimal gland involved [30]. Larger masses encase and infiltrate other orbital structures [21]. MR characteristics are a T1 hypo to isointense and T2 hypointense mass with homogeneous enhancement and restricted diffusion [31, 32] (Fig. 2).

The clinical features and imaging characteristics of orbital lymphoma may overlap with idiopathic orbital inflammation (IOI), which can make the distinction challenging. Eissa et al. found that the use of DWI (diffusion-weighted imaging) and ASL (arterial spin labeling) can be helpful. Lymphoma shows higher ASL values (hyperperfusion) and lower ADC (apparent diffusion coefficient) values in contrast to IOI which shows lower ASL values (hypoperfusion) and a higher ADC [33•]. Purohit et al. states that orbital lymphoma can be differentiated from IOI by using an ADC threshold of 1.0×10^{-3} mm^2/s, lymphoma shows values below this threshold and IOI values

above. This can also be used for differentiating between lymphoma and IgG4-related orbital disease or metastases, the latter show ADC values above the mentioned threshold [30].

Idiopathic Orbital Inflammation (IOI)

Idiopathic Orbital Inflammation (IOI) was previously known as orbital pseudotumor. This condition has a quick onset and is a diagnosis of exclusion [11]. After GO and lymphoproliferative disorders, IOI is the most common orbital disease [34, 35]. Patients with IOI typically present with acute pain, erythema, proptosis, diplopia, orbital swelling and decreased eye movement [10, 16]. The inflammation can occur in various tissues such as the lacrimal gland, anterior part of the globe, retro-orbital tissue or the extraocular muscles (myositis). The extraocular muscles are most frequently affected [33•].

The characteristic appearance of IOI myositis is unilateral extraocular muscle enlargement, affecting muscles in any order and including the tendinous insertion [10, 16]. The most affected muscle is the medial rectus, followed by the superior rectus, lateral rectus and inferior rectus [16, 17]. Sometimes the signs are atypical with more than one affected muscle and cases with bilateral muscle involvement and sparing of the tendons as in GO have also been reported [21]. Soft tissue stranding in the orbital fat is usually present in addition to the muscle enlargement [10]. The disease may spread to the cavernous sinus, superior orbital fissure, meninges or dura.

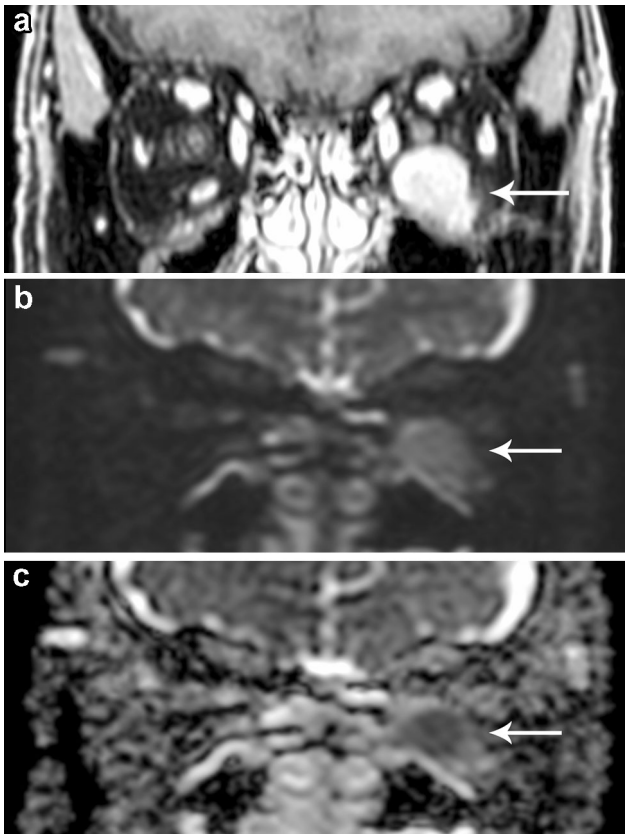

Fig. 2 Low-grade non-Hodgkin lymphoma. **a** Coronal post-contrast fat-suppressed T1-weighted image shows diffuse homogeneous increased enhancement of an enlarged left inferior rectus muscle (arrow). Coronal B1000 (**b**) and ADC images (**c**) show restricted diffusion of the lesion in the left inferior rectus muscle (arrow)

CT imaging shows enlargement and enhancement of the extraocular muscles, but also enhancing soft tissue, fat stranding, lacrimal gland enhancement and optic nerve sheath enhancement may be present [30]. On MR imaging the extraocular muscles are usually T1 hypo to isointense and T2 hypointense due to fibrosis, although T2 hyperintensity may also be seen [32, 36]. There is increased enhancement after contrast administration and no restricted diffusion. (Fig. 3). ASL shows hypoperfusion [33•].

Orbital Cellulitis

Orbital cellulitis starts acute and can progress rapidly. It is an infection with the usual signs as fever, pain, eyelid edema, proptosis, restricted motility and sometimes visual loss. Orbital cellulitis is frequently associated with a history of sinusitis, but also with recent dental care, orbital fracture, scleral buckling or recent eye surgery [32]. In post-septal cellulitis, extraocular muscles may be involved and show edema (Fig. 4). Due to its close contact with the ethmoidal sinus, the medial rectus muscle is mostly affected [2, 14]. The disease is usually unilateral. Complications of cellulitis that can be observed on imaging are an abscess (subperiosteal, intraconal or intracranial), superior ophthalmic vein thrombosis and cavernous sinus thrombosis.

CT of the orbit is the imaging of choice since quick treatment needs to be started to avoid or treat complications. Characteristics are intraconal or extraconal fat stranding and possibly edema of the extraocular muscles. MR shows T2 hyperintensity of the intra-orbital fat, variable enhancement and no restricted diffusion, unless complicated by abscess formation [32].

Metastasis

Metastases represent 2–3% of all orbital neoplasms [7•]. El Hadad et al. found that 60% of the 118 cases with orbital metastases were located in the extraocular muscles [37]. More than half (58%) of the patients diagnosed with metastases in extraocular muscles have a known primary malignancy at presentation [14, 21]. The most common primary tumors are breast cancer, melanoma, prostate cancer and gastrointestinal tumors [14, 38]. In general, the prognosis is poor [39].

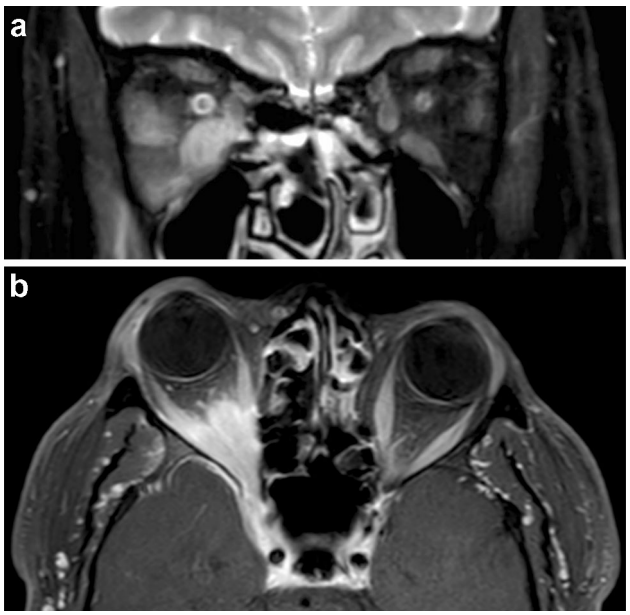

Fig. 3 IOI. **a** Coronal fat-suppressed T2-weighted image shows an enlarged and hyperintense right inferior rectus, lateral rectus, and to a lesser extent medial rectus muscle. **b** Axial post-contrast fat-suppressed T1-weighted image shows proptosis and increased enhancement of the lateral and medial rectus. There is also increased enhancement of the cavernous sinus and temporal right dura

Patients report diplopia, pain, restricted eye movement and proptosis [21, 40]. Most metastases are unilateral, bilateral cases are rare [39].

On imaging orbital metastases usually present as a focal mass in one or multiple muscles [2]. The lateral rectus muscle is the most vulnerable, possibly because this muscle gets more blood supply than the other muscles due to the lacrimal artery [41–43]. There is usually irregularity and nodularity of the enlarged muscle (Fig. 5). In most cases, there are other metastatic lesions nearby, for example in the bony orbit or intracranial. The affected muscle is usually T1 hypointense and T2 iso- to hyperintense, and shows homogenous enhancement and restricted diffusion [6•].

Vascular Etiologies

These include carotid-cavernous sinus fistulas, cavernous sinus thrombosis, dural-venous shunts and vascular malformations. All these vascular conditions can cause unilateral extraocular muscle enlargement. According to Shafi et al. there is usually enlargement of the horizontal rectus muscles (lateral and medial rectus), although sometimes only a single rectus muscle can be affected [14]. The muscle expansion is the result of tissue edema due to increased venous pressure and vascular distention [14, 44]. The severity of muscle enlargement is variable as it depends on flow dynamics [5].

Clinical signs are exophthalmos, conjunctival hyperemia and less frequently vision loss or paralysis of the extraocular muscles.

CT and MR can show venous dilatation, thickened extraocular muscles and fat stranding (Fig. 6). Due to venous congestion the muscles appear T2 hyperintense [7•].

IgG4- Related Ophthalmic Disease (IgG4-ROD)

This is an autoimmune disease with diffuse or tumefactive lesions filled with IgG4 positive plasma cells [2]. The orbit and salivary glands are the most frequent involved locations of the head and neck [19•]. The clinical signs are nearly similar to GO: patients present with eye lid swelling, proptosis, diplopia and decreased vision [45]. They have no or little pain and eye movements can be normal.

In IgG4 related orbitopathy, extraocular muscle disease is almost always accompanied by other manifestations, the

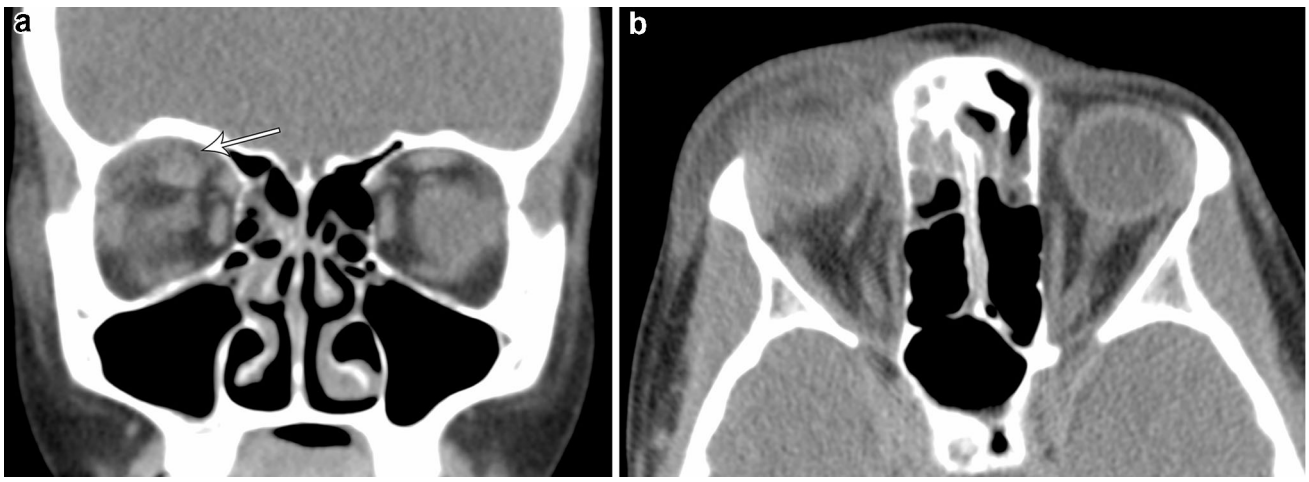

Fig. 4 Orbital cellulitis. **a** Coronal CT image shows an enlarged right superior rectus muscle (arrow) and post-septal fat stranding in the right superior-lateral quadrant of the orbit. **b** Axial CT image shows induration of the subcutaneous and pre-septal fat around the right orbit and to a lesser extent post-septal fat stranding

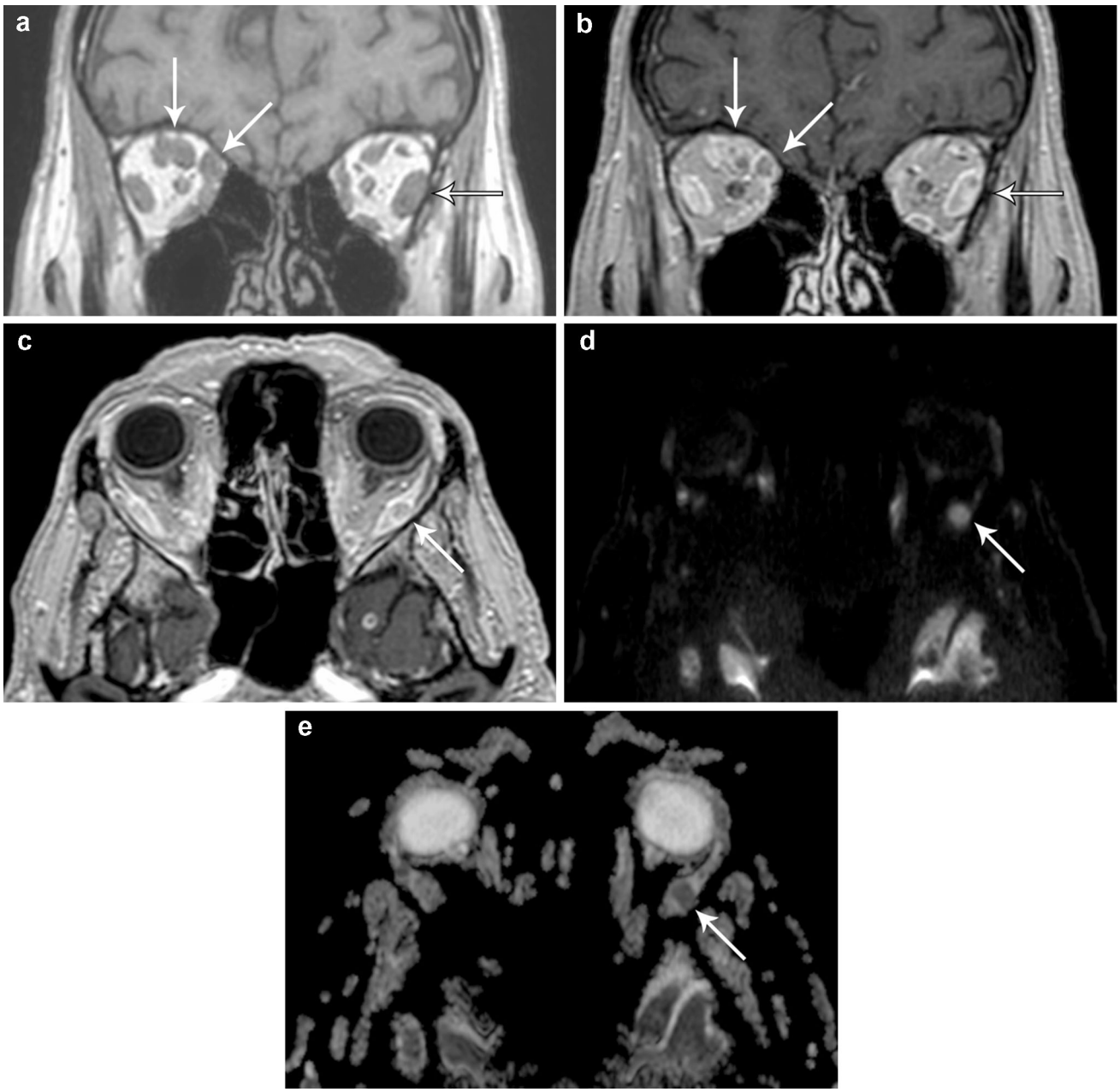

Fig. 5 Orbital metastasis. **a** Coronal T1-weighted image shows an enlarged left lateral rectus muscle, right superior rectus muscle, and superior oblique muscle (arrows). **b** Coronal post-contrast T1-weighted image shows focal lesions with rim enhancement in the enlarged muscles (arrows). **c** Axial post-contrast T1-weighted image shows one of the lesions in the left lateral rectus muscle with rim enhancement (arrow). Axial B1000 (**d**) and ADC images (**e**) with restricted diffusion of the lesion in the left lateral rectus muscle (arrow)

lacrimal gland is the most commonly involved but there may also be paranasal sinus disease or infra- or supra-orbital nerve enlargement [13, 19•, 46]. Furthermore, multiple other organs can be affected, e.g., salivary glands, pituitary gland, thyroid gland, lungs, pancreas, biliary ducts and retroperitoneal tissue [12]. As with GO, involvement is usually bilateral and does not involve the tendinous part. In contrary, the lateral rectus is the most affected muscle and the inferior rectus and medial rectus are often spared [11, 12].

On MR T1 and T2 hypointense and enhancing soft tissue is present [30]. Since lymphoma shows the same MR features, the ADC threshold can be used to differentiate. As previously described IgG4-ROD shows a higher ADC than lymphoma. A very helpful sign is enlargement of the trigeminal nerve, especially the infraorbital nerve [12, 45] (Fig. 7).

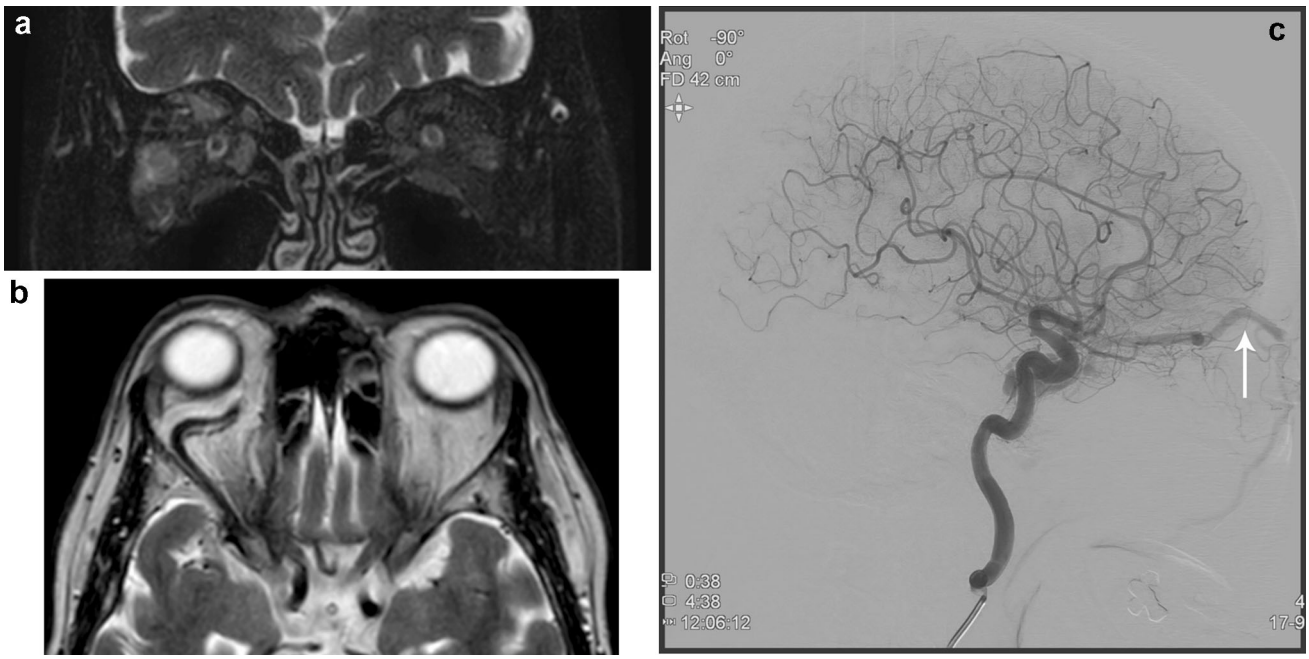

Fig. 6 Carotid-cavernous fistula. **a** Coronal fat-suppressed T2-weighted image with slight enlargement of the right extraocular muscles and subtle increased hyperintensity. **b** Axial T2-weighted image shows a dilated right ophthalmic vein. **c** Lateral angiography view shows early contrast in the dilated right superior ophthalmic vein (arrow), confirming a right-sided carotid-cavernous fistula

Sarcoidosis

Isolated myositis is rare in sarcoidosis, there are less than 20 case reports [15]. Sarcoidosis is a systemic inflammatory disease with granulomas in various organs. Involvement of the orbit is seen in 25–60% of the patients and uveitis is the most common manifestation [11, 47].

Patients present with diplopia, proptosis, reduced eye movement and the presence of pain is variable [13, 21]. Extraocular muscle involvement is usually bilateral [7•]. There is fusiform enlargement of the muscles, but sometimes also involvement of the tendons. The most likely affected muscles are the levator palpebrae muscle, superior rectus and lateral rectus. This preference is probably be due to neighboring dacryoadenitis [15].

The involved muscles are hypointense on T2, show enhancement and no restricted diffusion, these findings do not differ from GO. The lacrimal gland is enlarged in about 7–16% of cases [48]. There may be optic nerve thickening and enhancement or multiple pseudotumoral orbital masses [30]. A radiological clue to the diagnosis may be the visible involvement of the salivary glands or intracranial lesions [10, 21].

Other Conditions

There are more diagnoses that may have extraocular muscle enlargement, but these are rare and usually hard to distinguish based on imaging. Some of these rare diseases are briefly described in this paragraph.

Granulomatosis with Polyangiitis (GPA)

Also known as Wegener's granulomatosis. This vasculitis is necrotizing and mainly affects the small- and medium sized vessels. About 45% of the patients with GPA have orbitopathy and in 12% it is the initial manifestation [7•]. Ocular involvement in GPA can affect every structure of the eye and in 4–10% of the patients with orbital GPA, there is involvement of the extraocular muscles (orbital myositis) [49]. The GPA masses are usually unilateral. CT can show diffuse inflammation with bone destruction. MR shows T1- and T2-weighted hypointense enhancing lesions [50]. Most importantly, imaging is not always specific for GPA. Biopsy is frequently needed [51].

Amyloidosis

In amyloidosis there is accumulation of amyloid protein in tissues. Depositions in the extraocular muscle are rare: only 1.3% of orbital amyloidosis occurs in the extraocular muscles [52]. All muscles may be affected and can show fusiform enlargement with tendon sparing or irregular nodularity [53, 54]. MR shows T2 hypointense foci and T1 hypointense or isointense foci and contrast enhancement.

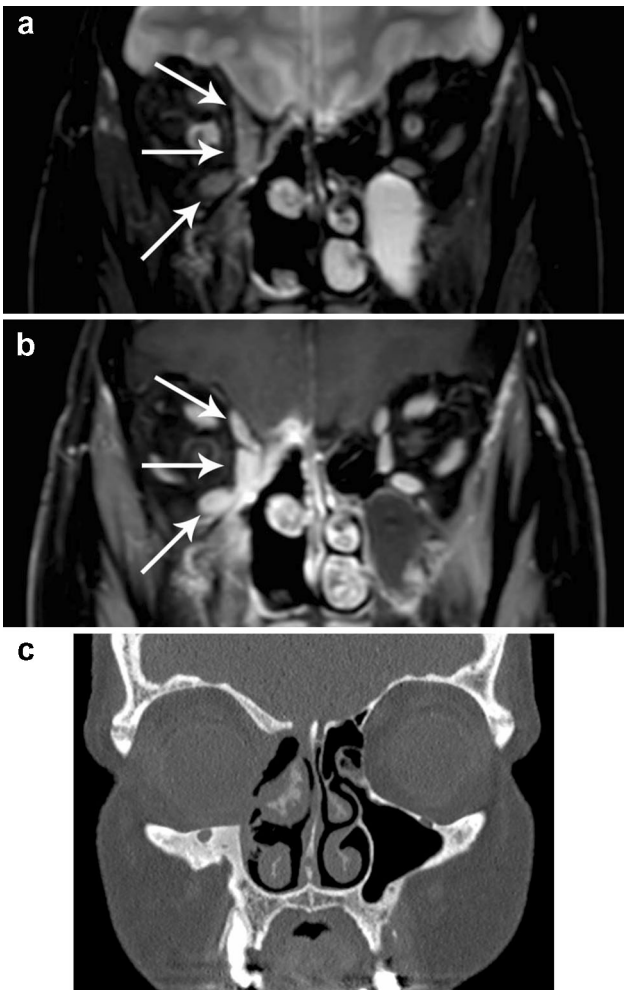

Fig. 7 IgG4-ROD. **a** Coronal fat-suppressed T2-weighted image shows enlarged inferior rectus, medial rectus, and superior oblique muscle (arrows) with slight hyperintense signal. **b** Coronal post-contrast fat-suppressed T1-weighted image shows increased enhancement of the right-sided enlarged muscles (arrows). There is also enhancement of the soft tissue in the nasal cavity and soft tissue expanding through the bone defects of the lamina cribrosa. **c** Axial CT image shows a bone defect of the right medial orbital wall and right orbital floor and an enlarged right infraorbital foramen

CT can show calcifications in the extraocular muscles, adjacent hyperostosis and bony irregularity [54, 55].

Specific Orbital Myositis

Specific orbital myositis is less common than idiopathic orbital myositis and accounts for about 5% of the orbitopathy cases [21]. This is myositis that is secondary to a disease or condition. This may be a systemic disease such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), giant cell myocarditis, rheumatoid arthritis, Churg Strauss syndrome and Behçet disease [13, 56–58]. It can also be the result of an infection such as herpes zoster ophthalmicus, Lyme disease and cysticercosis [13]. And lastly, there is an association with medication such as ipilimumab, alemtuzumab, bisphosphonates, statins, Interferon α-2b and ribavirin and infliximab [13, 59]. The extraocular muscles are enlarged on imaging and show a T2 hyperintense signal.

Acromegaly

As part of the generalized organomegaly, the extraocular muscles may also be enlarged in patients with excess growth hormone secreting pituitary tumors. The extraocular muscles may be diffuse and symmetrically enlarged or some muscles may be spared [5, 60].

Conclusion

Extraocular muscle enlargement is due to GO in 95% of the cases, and recognizing alternative causes of muscle enlargement can be challenging. We propose 'red flags' that suggest alternative diagnoses. These red flags are signs that are atypical for GO: unilateral disease, atypical pattern of muscle involvement, adjacent structure involvement, restricted diffusion, and absence of pain. The most important and common alternative causes of extraocular muscle enlargement are lymphoma, IOI, orbital cellulitis, metastasis, vascular etiologies, and IgG4-ROD.

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Compliance with Ethical Guidelines

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Research Involving Human and Animal Participants This article does not contain any studies with human or animal subjects performed by any of the authors.

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