Diagnosis of enlarged extraocular muscles: when and how to biopsy

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Purpose of review
To review current knowledge regarding diagnosis of nonthyroid orbital disorders with extraocular muscle enlargement.

Recent findings
Recent publications have focused on immunoglobulin G4-related disease as a possible cause of enlarged extraocular muscles, on patterns of strabismus that raise a clinical suspicion of intramuscular lymphoma, and on surgical techniques to access the muscles for tissue biopsy.

Summary
With enlarged extraocular muscles, features to distinguish between competing diagnostic possibilities are based on imaging in the context of history and clinical signs. Infraorbital nerve enlargement in the presence of muscle enlargement strongly favours a diagnosis of immunoglobulin G4-related disease and reactive lymphoid hyperplasia. As our understanding of minimally invasive orbital surgery evolves, the diagnostic focus is shifting toward earlier identification through muscle biopsy.

Keywords
biopsy, diagnosis, extraocular muscles, immunoglobulin G4-related disease, thyroid eye disease

INTRODUCTION

Although most commonly occurring in thyroid eye disease, enlarged extraocular muscles are not specific for this condition and may occur with other processes such as inflammatory disorders (including the recently described immunoglobulin G4-related disease; IgG4-RD), neoplasms (including metastatic disease), vascular lesions, infections, and metabolic abnormalities [1,2]. Moreover, muscle enlargement due to a nonthyroid cause may very rarely arise alongside preceding, much commoner, thyroid muscular enlargement. Symptoms of muscular enlargement are often nonspecific and include orbital 'ache', double vision, eyelid swelling, change in position of the eye, ocular redness and tearing.

In light of the diagnostic challenges that frequently accompany patients presenting with enlarged extraocular muscles, a systematic approach is recommended to identify the cause, with muscle tissue biopsy being a critical option.

Recognizing nonthyroid muscular enlargement

The process of diagnosis starts with categorizing the clinicoradiologic picture as 'thyroid' or 'nonthyroid' (Table 1 and Fig. 1). Notably, discrete muscle enlargement should not be confused with physiological expansion of the muscle diameter because of muscle contraction [3]. Unless part of a systemic condition, serum markers of inflammation, malignancy, or systemic disease have limited value, as they are often unchanged because of the very limited volume of extraocular muscle disease [4,5▪▪–7▪▪].

Patterns of muscular disease

Three patterns of muscular enlargement may be identified on imaging: single muscle, multiple muscles, and muscle changes with involvement of other orbital structures – herein, called 'muscle-plus' disease. The various orbital disorders with muscle enlargement may have common patterns of muscular involvement (Table 2).

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KEY POINTS

- Strabismus and imaging patterns help to identify which patients should undergo surgical muscle biopsy, and which patients can safely be treated empirically.
- Muscle biopsy should be considered in patients with a clear history of thyroid eye disease if the clinical course or imaging characteristics are atypical.
- Access to the extraocular muscles can be obtained through minimally invasive approaches with low-associated morbidity.

Table 1. Clinical and imaging features atypical of thyroid eye disease

Clinical	Imaging findings
Euthyroidism	Isolated or disproportionally enlarged muscle
No upper eyelid retraction	Enlarged superior rectus muscle with normal sized levator palpebrae superioris muscle
Strictly unilateral	Nodularity/intramuscular focal mass
Markedly asymmetric bilateral	Heterogeneous enhancement
Weakened muscle function	Tendon involvement
Pain	Infiltration of orbital fat
	Enlarged orbital nerve
	Enlarged superior ophthalmic vein
	Enlarged lacrimal gland
	Sinus disease

Single muscle enlargement is suggestive of idiopathic orbital myositis when associated with acute onset of marked orbital pain, particularly on eye movement, and often with a mild prodromal 'ache' the days before. With typical presenting symptoms and signs, an immediate trial of high-dose corticosteroids – without prior biopsy – is warranted, although a constellation of autoimmune phenomena may suggest other pathology – including the rare, but potentially life-threatening, giant cell myositis [8,9]. Where pain is absent, and with less acute presentation, malignant cause, such as lymphoma and metastasis, becomes more likely [2]. The commonest lymphocytic disorders affecting extraocular muscles are non-Hodgkin's B-cell lymphoma (predominantly marginal zone) and, less commonly, reactive lymphoid hyperplasia; rare lymphocytic disorders include T-cell lymphomas, leukaemias, and plasmacytomas (Fig. 2) [4,10–13]. Metastatic malignancies tend to affect the lateral rectus, this possibly being because of the comparatively rich additional supply from the lacrimal artery (being larger than arteries to the other muscles), or – as in leukaemia – because of the greater bone marrow density in the neighbouring greater wing of the sphenoid and zygoma [12,14]. In thyroid eye disease, isolated single muscle involvement is rare and, in practical terms, never affects the lateral rectus, superior rectus, or oblique muscles in isolation [15▪▪]. Where ocular motility is impaired, the pattern of such impairment aids in identifying the likely cause. Thus, a restrictive pattern is a feature of both thyroid and metastatic muscles, whereas paresis is indicative of lymphoid and nonthyroid

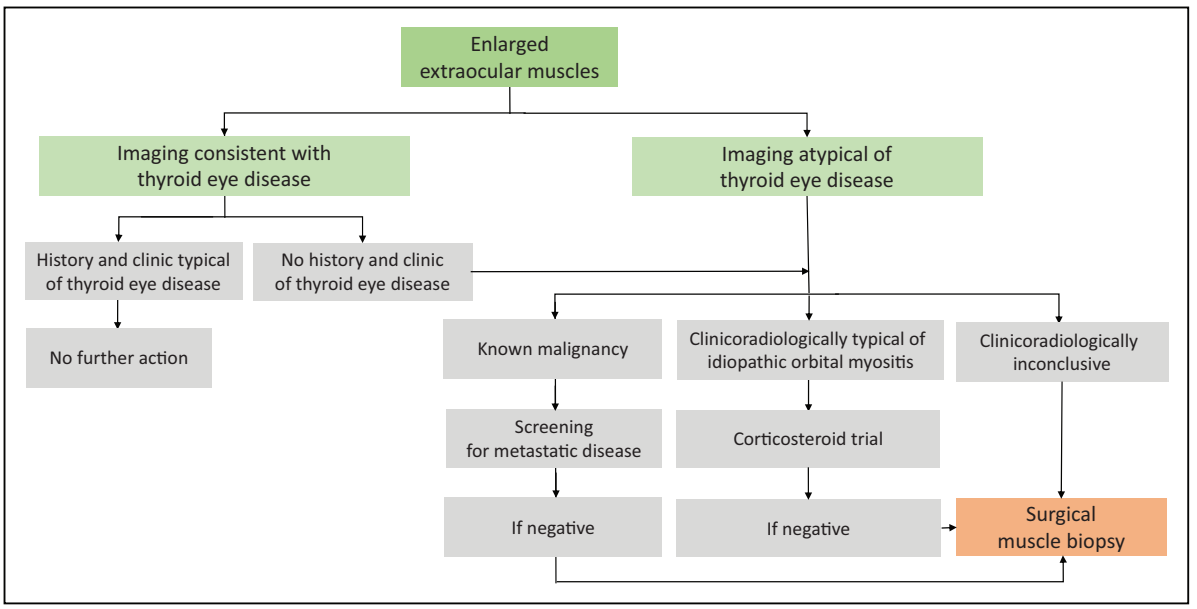

FIGURE 1. Algorithm for the diagnosis of enlarged extraocular muscles.

Table 2. Summary of orbital diseases affecting the extraocular muscles and their muscle patterns

	Clinical condition	Single muscle involvement	Multiple muscle involvement	'Muscle-plus' disease (in combination with single or multiple muscle involvement)
Inflammatory	Thyroid eye disease	IR or MR or LPS	IR, SR/LPS, MR or all muscles, often bilateral	Increase in orbital fat; lacrimal gland swelling
	Idiopathic orbital myositis	LR or MR	Any combination, often bilateral	
	IgG4-related disease	LR[a]	All muscles with LR most enlarged, often bilateral[a]	Enlarged orbital nerves; sinus disease; lacrimal gland masses
	Giant cell myositis		MR, LR; or all muscles, bilateral	
	Sarcoidosis Granulomatosis with polyangiitis[a]	Any muscle	Any muscles	Lacrimal gland swelling; nasosinal disease (GPA)
	Paraneoplastic orbital myopathy[b]	MR or SR	All muscles, bilateral (lymphoma)	Lacrimal gland swelling (thyroid carcinoma)
	Orbital cellulitis	Any muscle[a]	Any muscles[a]	Adjacent sinus, orbital, or lacrimal gland infection
Neoplastic	Lymphoma	Any muscle	Any combination of IR, MR, LR, SR, LPS occasionally bilateral	Lacrimal gland swelling; mass parietal to the orbital wall; enlarged orbital nerves; sinus disease
	Metastasis[c]	Any muscle	Any combination, or all muscles, occassionally bilateral	
	Locally invasive	Any muscle[a]	Any muscles[a], occasionally bilateral	Adjacent infiltrative orbital or sinus process; bony erosion
Deposition	Amyloidosis	Any muscle	Any muscles, bilateral[a]	Adjacent infiltration of the orbital tissues
Vascular	Orbital venous congestion		All muscles[a]	Enlarged superior ophthalmic vein; apical mass
	Muscle haematoma	Any muscle		Adjacent haematoma

GPA, granulomatosis with polyangiitis; IR, inferior rectus muscle; LPS, levator palpebrae superioris muscle; MR, medial rectus muscle; SR, superior rectus muscle.
[a]Always in combination with 'muscle-plus' disease.
[b]Breast carcinoma, thyroid carcinoma, lymphoma.
[c]Breast carcinoma, melanoma, lung carcinoma, carcinoid, prostate carcinoma, renal cell carcinoma, pancreatic carcinoma, gastrointestinal carcinoma, thyroid carcinoma.

inflammatory muscles, or can result from a mass effect [16]. Hence, in a patient with thyroid eye disease, painless medial rectus enlargement associated with an adduction defect is suggestive of lymphoma, despite a known history of thyroid dysfunction [17]. However, in some patients the involvement is subclinical and does not produce ocular motility dysfunction.

The multiple muscle enlargement of the inferior and medial rectus with the superior rectus/levator complex, often regarded as pathognomonic for thyroid eye disease, is not always reliable as this pattern may also occur in lymphoma, reactive lymphoid hyperplasia, IgG4-RD, myositis and metastases (Fig. 3) [16–19]. Enlarged and tight recti in childhood may represent the muscular variant of congenital orbital fibrosis, (eu)thyroid eye disease, or a separate – as yet unidentified – entity [20,21].

'Muscle-plus' disease is present where there are additional alterations in the vasculature, soft tissue, or bony orbital structures. Orbital fat infiltration and a nodular appearance to the enlarged extraocular muscles suggest secondary infiltration from contiguous soft tissue, bony, and sinus disease, with the infiltration being of malignant, inflammatory or infectious origin (Fig. 4). Enlarged lateral and superior recti may be associated with benign and malignant lacrimal gland tumours, and lateral and inferior recti with sphenoid wing meningioma [22,23]. Enlarged orbital nerves – particularly the infraorbital – or a mass within the orbital fat or lacrimal gland, is highly suggestive of IgG4-RD and lymphoid hyperplasia [24,25▪▪]. IgG4-RD most commonly and dramatically affects the lateral rectus, and often presents with associated sinus disease (Fig. 4) [26,27]. Enlarged muscles associated with a widened superior orbital fissure suggest neurofibromatosis [1].

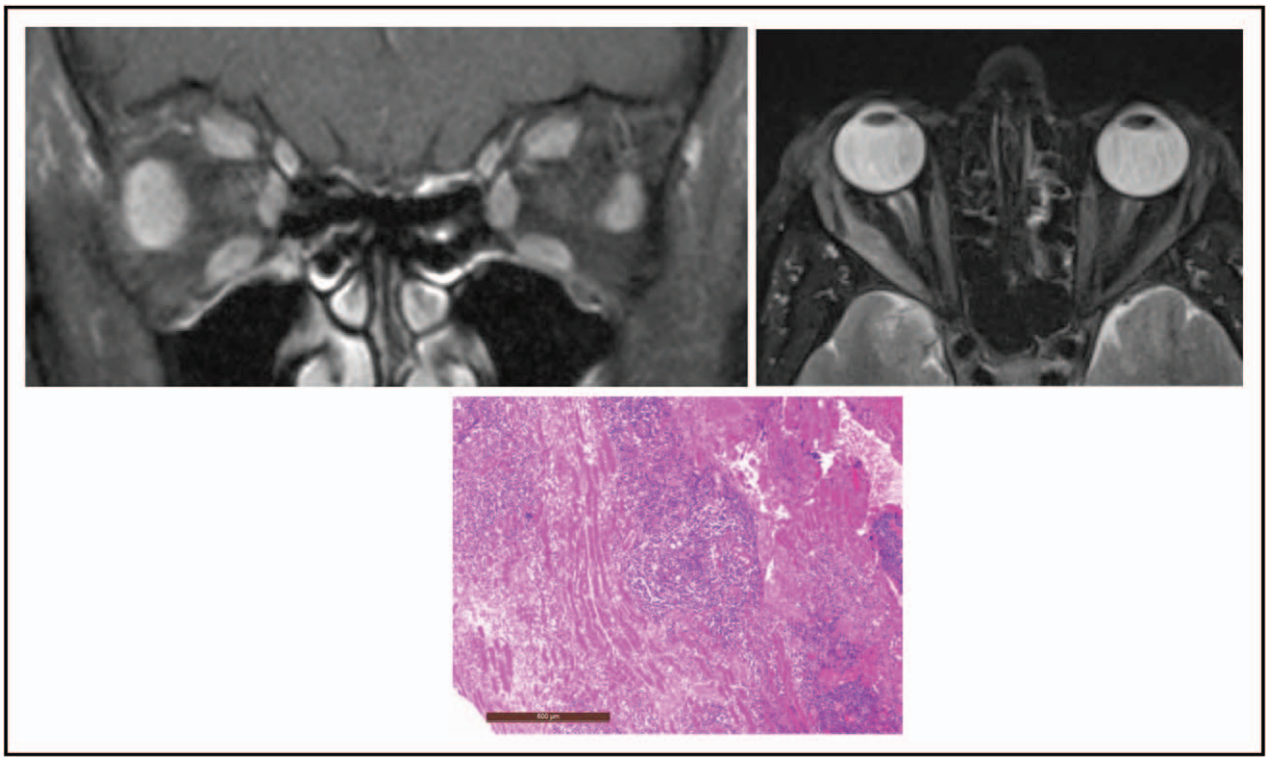

FIGURE 2. Single muscle enlargement, reactive lymphoid hyperplasia. (Top left) coronal and (top right) axial computerized tomography showing right tendon-sparing lateral rectus muscle enlargement. (Bottom) Muscle biopsy of the same patient, obtained via canthotomy approach to anterior orbitotomy, demonstrating the architecture of muscle fibers with a dense lymphoid infiltrate organized in lymphoid follicles (Hematoxylin and eosin; original magnification x 50). Polymerase chain reaction studies did not detect clonal rearrangements of the immunoglobulin heavy chain (IgH), immunoglobulin light chain (IgK), T-cell receptor β and γ genes, and IgG4 immunohistochemistry was negative.

Muscular features

With orbital imaging, the differential diagnosis can further be narrowed by signal intensity, contrast enhancement, shape, presence or absence of tendon involvement, and structure and border. Extraocular muscles normally appear dark on T1 and T2-weighted MRI: a hyperintense T2 signal usually arises from inflammation and tumour because of increased intra and extracellular fluid, whereas a low signal indicates fibrosis. Inflammation, infiltration, and venous congestion of a muscle causes gadolinium enhancement, with heterogeneity favouring malignancy.

Although fusiform muscular enlargement is common and diagnostically nonspecific, involvement of the anterior tendon may favour certain disorders – being frequently seen in idiopathic orbital myositis and giant cell myositis, less often in lymphoma, but, infrequently occurring in severe thyroid eye disease (Fig. 3) [8,9,16,28].

Structural changes within a muscle – such as irregular edges, nodularity or a focal intramuscular mass – are strongly indicative of malignancy, although nodularity is also seen in amyloidosis. In contrast, the presence of fat within an enlarged muscle is generally benign, as adipogenesis is specific to longstanding thyroid eye disease [29].

MUSCLE BIOPSY

A muscle biopsy is warranted where clinicoradiologic findings are inconclusive, or to substantiate a putative diagnosis – particularly in the absence of known metastatic or systemic disease. Any increased surgical risk should be balanced against the significant risk of delayed diagnosis in the absence of a tissue diagnosis; inadvertent immunosupression for a presumed diagnosis of 'pseudotumour' in the presence of undiagnosed neoplasia carries a major risk of untreated and progressive systemic disease [8,30].

Morphological aspects of normal extraocular muscles

The rectus muscle fibres have a layered organization, with an orbital layer facing the orbital walls, and a global layer facing the globe. The motor nerves enter the global layer near the junction of the middle and

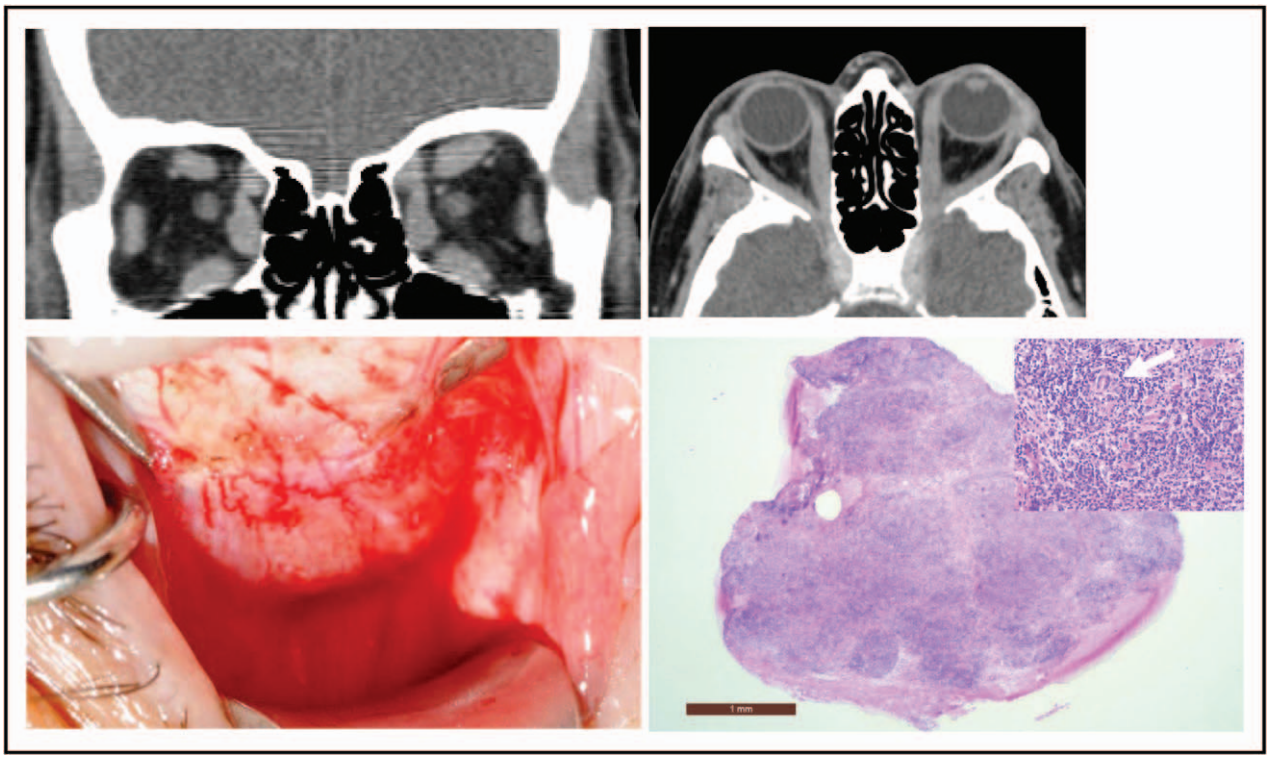

FIGURE 3. Multiple muscle enlargement, giant cell orbital myositis. (Top left) coronal and (top right) axial computerized tomography demonstrating diffuse enlargement of multiple muscles including the anterior tendons, with no involvement of the right superior rectus and levator muscles. (Bottom left) Surgical view of the enlarged left medial rectus muscle, using a limbal incision under local anesthesia. (Bottom right) Histopathology of the same patient, showing abundant infiltration of histiocytes, lymphocytes and eosinophils (Hematoxylin and eosin; original magnification x 16), with multinucleated giant cells (arrow) surrounding degenerated muscle fibers (Inset; Hematoxylin and eosin; original magnification x 100). The fungal stains were negative, and gene rearrangement studies of IgH and IgK showed no evidence of clonality.

posterior one-third, and divide into branches that pass toward both ends of the muscle. When interpreting biopsy results, it is important to acknowledge the population of immunocompetent cells normally resident within the extraocular muscles: these include T cells and macrophages, with twice as many macrophages in the medial and inferior recti as in the lateral rectus and superior oblique muscles [31]. B lymphocytes and plasma cells (such as IgG4-positive plasma cells) are not present in healthy muscles, and with increasing age there is endomysial fibrosis, loss of myofibrils, accumulation of lipofuscin, and reduction in fibre density [32].

Surgical technique for muscle biopsy

Where multiple muscles are affected, a tissue biopsy can be obtained from any involved muscle, but the surgical morbidity to the inferior oblique and the inferior and medial rectus is lower than to the superior and lateral rectus muscle [33]. In 'muscle-plus' disease, biopsies from both the affected muscle and the extramuscular mass are required, typically through the same incision, to be representative. Forced duction testing before and during surgery may be contributory to diagnosis and, with restrictive strabismus, the biopsy might be combined with simultaneous squint surgery.

The anterior half of a rectus muscle can be accessed through strabismus surgery approach, by placing a conjunctival incision – depending on the friability of the conjunctiva – in the fornix or at the limbus. A muscle hook is passed around the insertion, and many anteriorly located biopsies can be performed under local anaesthesia. However, where the pathology lies within the posterior half of the muscle, access is best obtained via an orbitotomy approach, this giving better 'en face' access to the deeper tissues compared with a strabismus surgery approach which affords a more 'end-on' view. Thus, to biopsy the posterior half of the lateral rectus muscle, a lateral canthotomy approach gives the best access (Fig. 5) [34]. To biopsy the inferior rectus, this approach is extended with a lower cantholysis to form a swinging lower lid flap of varying degree,

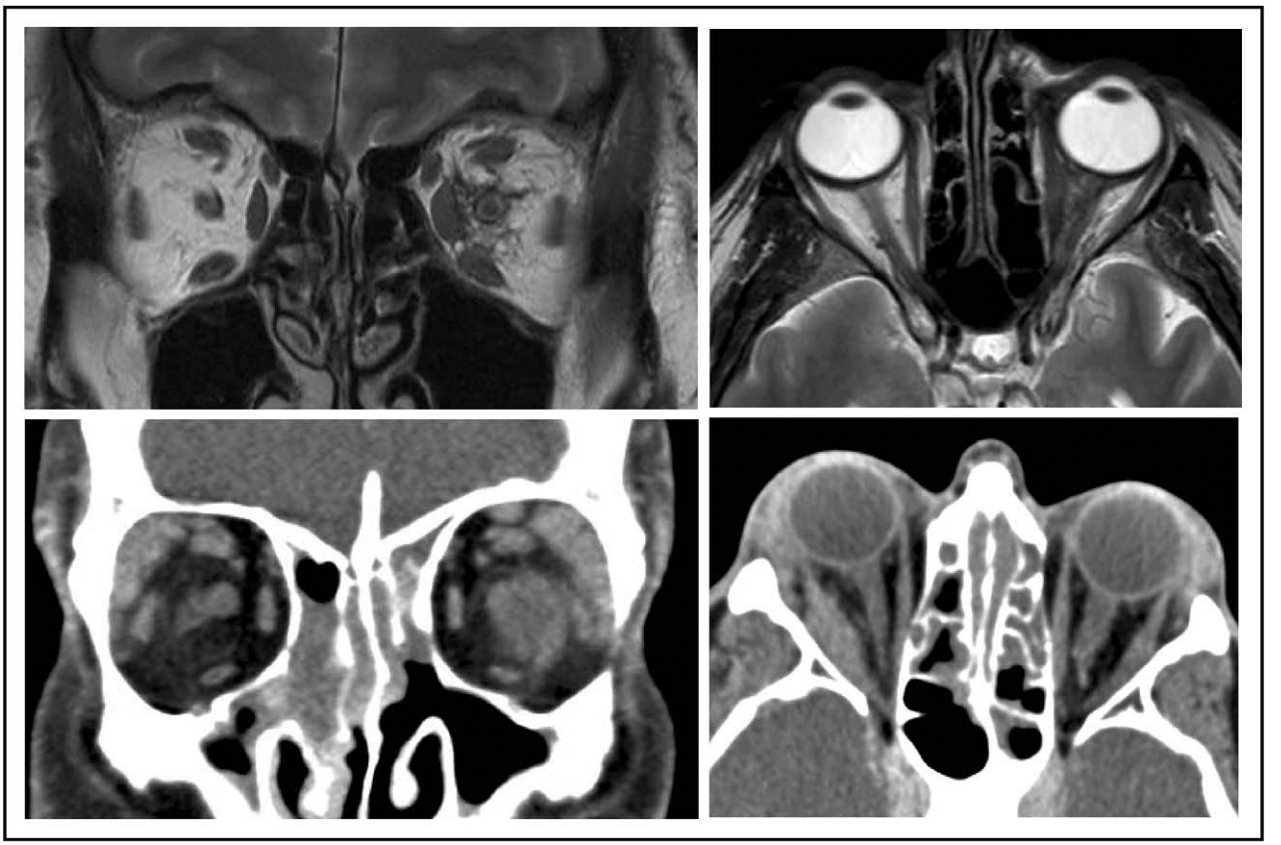

FIGURE 4. 'Muscle-plus' disease. (Top left) coronal and (top right) axial view of MRI of metastasis of breast adenocarcinoma, showing left enlarged medial rectus muscle and soft tissue densities infiltrating the intraconal fat space, in a patient with known metastatic disease. (Bottom left) coronal and (bottom right) axial MRI of a patient with immunoglobulin G4-related disease, demonstrating right tendon-sparing lateral rectus muscle enlargement, bilateral lacrimal gland enlargement, and paranasal sinus disease with sequelae of previous sinus surgery.

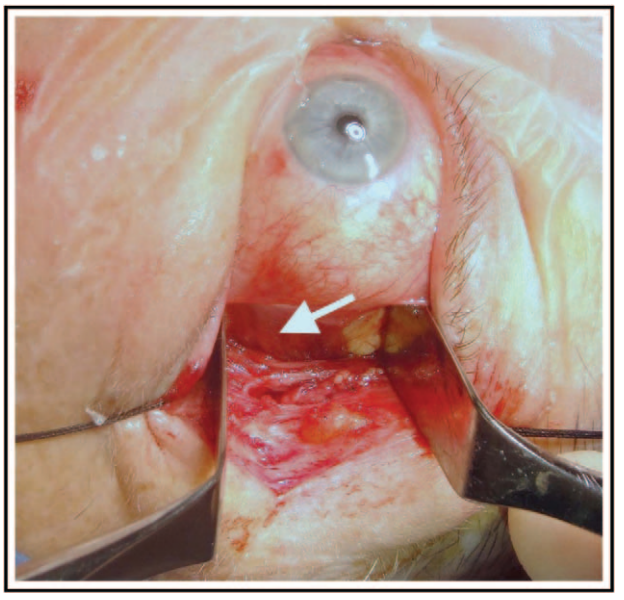

FIGURE 5. Lateral canthotomy approach to anterior orbitotomy. Surgical view of lateral rectus muscle (arrow).

depending on the exposure required [34]. The latter approach gives excellent access both to the muscle(s) and any adjacent pathology, and in no cases is a bone-swinging lateral orbitotomy ever indicated.

Because of restricted access to the deep superior rectus/levator complex, this area is best accessed via an upper eyelid skin-crease approach anterior orbitotomy. Where a biopsy of the superior rectus itself is indicated, the levator muscle is displaced medially to expose the surface of the underlying superior rectus, with direct traction on the muscle resulting in globe elevation and confirming its identity. In such cases, biopsy is not infrequently complicated by a marked upper lid ptosis, with complete resolution typically occurring over several months. Finally, a mid-to-posterior medial rectus muscle biopsy is best achieved via a retrocaruncular route, with the enlarged muscle belly clearly exposed between two paddle retractors placed above and below the medial rectus to separate the tissues.

Biopsies should be directed to visibly abnormal tissue and, with the muscle stretched, the biopsy

should be taken parallel to the long axis and from the orbital layer of the muscle, thereby avoiding damage to the motor nerves. The first-obtained specimen should be adequately large, as a second biopsy tends to be affected by haemorrhage, crush, or heat artefacts. To avoid traumatic artefacts in the biopsy, it is best to use toothed forceps, grip the specimen once only, and refrain from intramuscular injection of local anaesthetic agents. Biopsies taken alongside the site of the conjunctival or periosteal incision carry a risk of adhesion syndrome, this being less likely in biopsies taken in the posterior part of the muscle where fat naturally spills around the biopsy site.

Preoperatively, it is essential that systemic or intralesional corticosteroids should be avoided for at least 2 weeks prior to obtaining the biopsy, as they may significantly affect the histopathology and its interpretation. Rebiopsy should be considered where biopsy fails to identify the disease but clinical suspicion for major pathology remains high [8].

CONCLUSION

A structured approach helps identify the cause of enlarged extraocular muscles, with differentiation of nonthyroid from thyroid-related pathologies through detailed clinical examination and diagnostic imaging. Because of the risk of malignancy, a muscle biopsy is required where the clinicoradiologic picture is inconclusive for diagnosis, or where the clinical behaviour changes or fails to respond to treatment. With the correct approach, biopsy of the muscles carries a low morbidity and helps to refine the diagnosis, the histology usually identifying which further route(s) of investigation are necessary.

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Conflicts of interest

There are no conflicts of interest.

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