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# Review article: Diagnosis and management of enlarged extraocular muscles

**Mahmoud Mostafa Abouelatta[1,2*], Osama El Saied Shalaby[1], Amr Mahmoud Awara[1], Don Osami Kikkawa[2], Mohammed Ashraf Eldesouky[1]**

**Abstract:**

Extraocular muscle (EOM) enlargement may be due to a variety of causes. These causes can be classified in three ways: according to pathogenesis and histopathological features, according to the site, and according to the clinical features. Diagnosis of the cause is dependent upon history, clinical examination, and investigations. Imaging with computed tomography or magnetic resonance imaging and muscle biopsy is typically necessary to make the correct diagnosis. Treatment of the patient must be directed toward the specific cause. This review emphasizes important clinical and pathological guidelines for appropriate diagnosis and treatment of patients with EOM enlargement.

**Keywords:**

Enlarged extraocular muscle, imaging, muscle biopsy, myositis

## Introduction

The four rectus muscles (superior, inferior, medial, and lateral) originate from the annulus of Zinn, a tendinous ring surrounding the optic foramen at the orbital apex.[1] They insert at different distances from the corneal limbus an imaginary line known as the spiral of Tillaux.[2] Two oblique muscles, the superior and inferior obliques, the superior oblique muscle originates from the orbital apex just above the origin of recti[3] and the inferior oblique originates from the orbital floor lateral to lacrimal sac fossa.[4]

The extraocular muscles (EOMs) act in coordination simultaneously to provide conjugate movement in various directions and to keep adequate alignment within the orbit. During contraction, rectus muscles tend to move the eye posteriorly because they are inserted anterior to the equator while the obliques provide a counterforce in the opposite direction because of insertion posterior to the equator.[5]

This review will focus on the causes, diagnosis, and management of EOM enlargement. A flowchart summarizes recommendations [Figure 1]. A thorough PubMed search was undertaken to complete the review.

## Classification of Extraocular Muscle Enlargement Causes

Several classification schemes have been described. In this article, we delineate categories according to pathogenesis and histopathological features, according to the extent, and according to the clinical features.

### Pathological classification

#### *Graves' disease*

Autoimmune thyroid orbitopathy is the most common cause of enlarged EOMs. There has been a recent comprehensive review article focusing on thyroid eye disease,[6] hence this review will focus on non-Graves causes of muscle enlargement.

*[1]Division of Oculofacial Plastic and Reconstructive Surgery, Department of Ophthalmology, Faculty of Medicine, Tanta University, Tanta, Egypt, [2]Division of Oculofacial Plastic and Reconstructive Surgery, Department of Ophthalmology, Shiley Eye Institute, University of California, San Diego, California, United States of America*

***Address for correspondence:**
Dr. Mahmoud Mostafa Abouelatta, Department of Ophthalmology, Faculty of Medicine, Tanta University, El Bahr Street, Tanta 31111, El Gharbia, Egypt.
E-mail: mahmoud.aboualatta90@med.tanta.edu.eg

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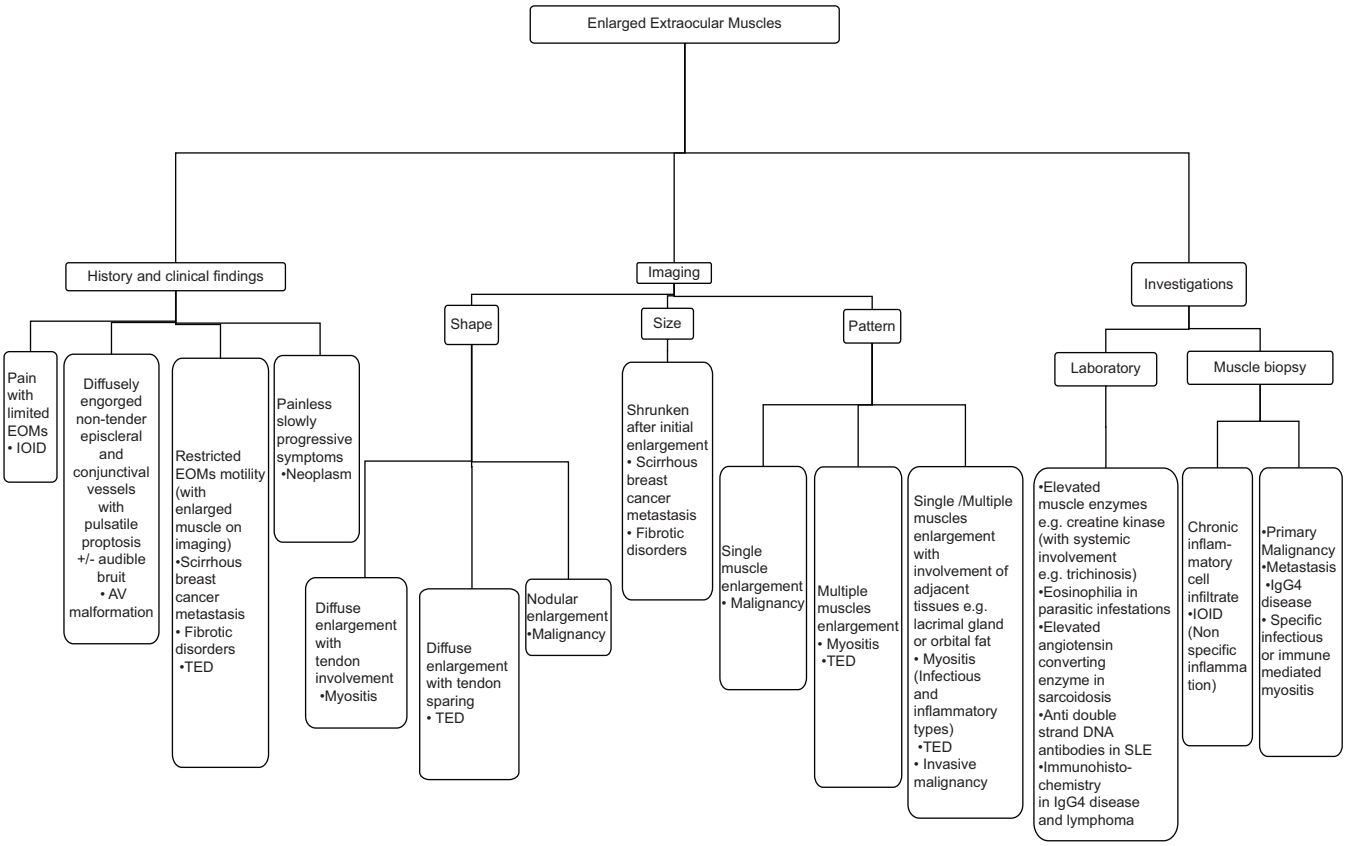


**Figure 1:** A flowchart summarizing classification of causes and diagnosis of enlarged EOMs. EOMs = Extraocular muscles

### *Specific causes of myositis*

Specific causes of myositis may occur because of infectious diseases, such as bacterial, viral, or parasitic diseases, or occur due to immune-mediated disorders.[7] Infectious diseases affecting EOMs are either due to a specific agent involving the EOM directly or due to spread from adjacent infection, particularly from paranasal sinuses. The medial rectus muscle is the most common muscle affected due to proximity to the ethmoid sinus.[8]

## Infectious-specific myositis

### Trichinosis

The nematode, *Trichinella spiralis,* can cause a parasitic myopathy which is from ingestion of the encysted larva present in undercooked or raw pork meat. Clinically, there may be periorbital edema, conjunctival chemosis, and limited painful motility of multiple skeletal muscles including extraocular, diaphragm, pectoral, and upper-limb muscles. Laboratory studies may show eosinophilia and elevated muscle enzymes in the serum due to systemic involvement. Radiographically, calcifications may appear in chronic cases.[9]

### Cysticercosis

Cysticercosis is a parasitic myopathy caused by the larval stage of *Taenia solium* which infects humans after ingestion of undercooked or raw pork meat.[9] Larval cysts may affect subcutaneous tissues, skeletal muscles, lungs, brain, eyes, liver, heart, thyroid, and pancreas.

### Lyme disease

Lyme disease is caused by a tick-borne infection by the spirochete, *Borrelia burgdorferi.* Clinically, it produces inflammation of different systems including skin, EOMs, central nervous system, cardiovascular system, and joints.[9]

### Whipple's disease

Whipple's disease is a rare multisystem infection caused by *Tropheryma whipplei*. Clinically, it is more common in middle-aged males, initially presenting with diarrhea and weight loss and later with arthritis, arthralgia, nervous system affection, and enlarged EOMs.[10]

### Tuberculosis

*Mycobacterium tuberculosis* can cause bacterial infection in the lungs and visceral soft tissues. Although rare to affect the orbit, miliary tuberculosis of the lacrimal gland may form a caseating granuloma that also may affect the EOMs.[9]

### Syphilis

The spirochete *Treponema pallidum* causes a sexually transmitted bacterial disease. Gummatous infiltrates may rarely invade the orbit.[9]

## Immune-mediated specific myositis

### Systemic lupus erythematosus

Lupus is a multisystem collagenic vascular disorder causing diffuse occlusive vasculitis primarily in the arterioles. It is more common in females. Classically, there are malar rash, photosensitivity, multiple organ system involvement, and possibly enlarged EOMs. Laboratory testing may reveal elevated anti-double-stranded DNA antibodies and other enzymes such as creatine kinase and aldolase. Patients may be treated with corticosteroids, hydroxychloroquine, and plasmapheresis.[9]

### Sarcoidosis

Sarcoidosis results from granulomatous inflammation that may be localized or affects multiple areas of the body. Clinically, it is more common in patients of African ancestry and may involve the EOMs as an isolated entity in absence of systemic disease or as a part of systemic disease. Enlarged EOMs may occur with or without pain, and association with uveitis and lacrimal gland inflammation is not unusual. Laboratory testing typically shows elevated serum level of angiotensin-converting enzyme and lysosome, proportional to the inflammatory burden on the body. Radiologically, chest imaging typically shows bilateral hilar lymphadenopathy. Histologically, noncaseating granulomatous inflammation containing epithelioid cells is present.[11]

### Crohn's disease

Crohn's disease is manifest by granulomatous inflammation of the small and large intestines. Clinically, gastrointestinal manifestations predominate, including vomiting, abdominal pain, and hematochezia, but extra-intestinal manifestations such as erythema nodosum, arthralgia, orbital inflammation, and enlarged EOMs may also be present.[9]

### Giant cell myositis

Giant cell myositis is a T-cell-mediated inflammatory disease affecting the skeletal muscles, heart, and EOMs.[12] Clinically, it may present with bilateral enlarged EOMs followed by congestive heart failure and progression to death.[9] Necrosis is commonly seen on histopathology.[12]

### Immunoglobulin G4-related orbital disease (immunoglobulin G4 disorder)

Immunoglobulin G4 (IgG4) inflammation is included in the spectrum of inflammatory orbital diseases. There is typically abnormally high serum level of IgG4 that involves orbital tissues, primarily the lacrimal gland and the EOMs. This immune-mediated reaction results in immune-mediated fibrocellular infiltration of EOMs by a dense fibrous infiltration. Infraorbital nerve enlargement is characteristic of the disease. Clinically, it affects EOMs with a gradual onset and a slowly progressive restriction of motility, onset of diplopia, and discomfort.[9] IgG4 disease can be diagnosed histopathologically by immunohistochemistry that detects the IgG4-positive cells in biopsy specimens.[13]

## *Nonspecific myositis*

Nonspecific myositis is the third most common cause of enlargement of EOMs following Graves' disease and lymphoproliferative disorders. It is a diagnosis of exclusion provided that all specific causes have been ruled out. It is caused by an autoimmune idiopathic noninfectious nonneoplastic inflammation of single or multiple EOMs. Although previously referred to as "orbital pseudotumor," the preferred term is now "idiopathic orbital inflammatory disease (IOID)." Multiple patterns of involvement may occur including EOMs, but patients may also present with dacryoadenitis, episcleritis, and perineuritis.[14]

Clinically, nonspecific myositis also has different clinical presentations according to the age of the patient. Adult patients present with restrictive motility in the field of action of the inflamed muscles with subsequent diplopia. Imaging is recommended in all patients that present with acute inflammatory signs and chronic resistant cases [Figure 2]. If the muscle involvement is associated with conjunctival injection, it is termed limited oligosymptomatic ocular myositis, while if diplopia is associated with proptosis, ptosis, and chemosis, it is termed severe exophthalmic ocular myositis.[7,15] Fifty percent of children present with fever, headache, lethargy, anorexia, and vomiting which are rare in adults, and bilaterality is reported in up to 45% of pediatric patients. Iritis and peripheral eosinophilia may also be present in children.[16] Intracranial extension is rare, but it may occur through the superior orbital fissure and involve cavernous sinus with subsequent marked reduction of vision and worsening of proptosis.[17]

Histopathologically, a pleomorphic inflammatory cell infiltrate that consists of lymphocytes, macrophages, polymorphonuclear leukocytes, and eosinophils admixed with edema and fibrosis is typically present.[18] When fibrosis occurs, which is uncommon, it is characterized by a slowly progressive course with less prominent clinical signs mimicking neoplastic lesions, and rarely, calcification may occur.[19]

Initial treatment is with systemic steroids, prednisone 0.5–1 mg/kg/day, by either oral or intravenous routes. With improvement of clinical manifestations, slow gradual tapering of steroids should occur. If symptom recurs, biopsy is recommended. Recalcitrant cases may be treated with radiotherapy; antimetabolites

such as methotrexate or mycophenolate mofetil; and immunomodulators such as cyclosporine, infliximab, or adalimumab. All agents have reported different side effects, especially among immunocompromised patients.[7,20]

### *Neoplastic lesions*

Primary or secondary neoplastic lesions may involve the EOMs. Primary neoplastic lesions are less common. Granular cell tumor is a primary benign neoplasm that arises from Schwann cells and involves the EOMs and other orbital tissues. Leiomyomas are benign tumors of myogenic origin. Rhabdomyosarcoma is most commonly in children under 13[21] and arises from the pluripotent mesenchymal cells within the orbital soft tissues. Rare cases of rhabdomyosarcoma may arise from the muscle itself. Meningioma and alveolar soft part sarcoma have been reported to affect EOMs.[8,9]

Secondary neoplastic lesions involving the EOMs are more common than primary ones. These lesions occur due to adjacent spread from nearby structures, e.g., sinus tumors, or due to metastasis. Due to robust circulation, almost any tumor may spread to the orbit, but orbital metastasis most commonly arises from breast carcinoma, malignant cutaneous melanoma, and gastrointestinal tumors, such as adenocarcinoma and carcinoid tumors. Bronchial, renal, and prostatic carcinomas can also spread to the orbit but less commonly [Figure 3].[22,23] Recently, metastatic seminoma in the orbit involving the EOMs has been reported.[24]

Infiltrative lobular breast carcinoma is the most common type of metastasis to the orbit.[24] Clinically, patients may present with ophthalmic manifestations including pain, diplopia, restricted ocular motility, and proptosis.[25,26] Some patients may present with enophthalmos with scirrhous breast cancer.[27]

Carcinoid tumors are neuroendocrine tumors arising from the enterochromaffin cells that are present mainly in gastrointestinal tract and liver, in addition to the bronchial tree. Clinically, patients may present with diarrhea, flushing, wheezing, and right-side heart failure. This constellation of symptoms is known as "carcinoid syndrome."[28] Orbital spread from carcinoid represents approximately 5% of metastatic orbital lesions, and usually, it occurs in advanced disease stages.[29]

Lymphocytic disorders that tend to involve EOMs constitute a broad range. The most common malignant type is the non-Hodgkin B-cell lymphoma (NHL – B-cell type) [Figure 4], and the most common benign type is reactive lymphoid hyperplasia. Less common types are T-cell lymphoma, leukemia, and plasmacytoma.[30] Lymphoma can involve multiple orbital structures, but when infiltrating EOMs, it is mostly unilateral and with single-muscle involvement.[31] Orbital lymphoma can exist locally or be present systemically.[32] The orbit is involved in only 1%–2% of all NHL patients.[33]

Plasmablastic lymphoma is a rare subtype of diffuse large B-cell lymphoma. It is highly fatal, occurring in immune-compromised patients infected most commonly by human immunodeficiency virus and Epstein–Barr virus. Clinically, patients present with painful restricted ocular motility, lid edema, ptosis, conjunctival chemosis, and systemic manifestations, especially oral cavity involvement.[34] Histologically, muscle infiltration is seen with medium-to-large-sized abnormal lymphoid cells with multiple nucleoli and irregular nuclear membranes.[35] Abnormal lymphocytes admixed with apoptotic bodies and macrophages containing debris are also seen. Immunohistochemistry reveals CD138, CD38, and CD79a positivity and negative staining for CD19 and CD20.[35]

Paraneoplastic syndromes are rare entities that may occur in patients diagnosed with systemic malignancies.

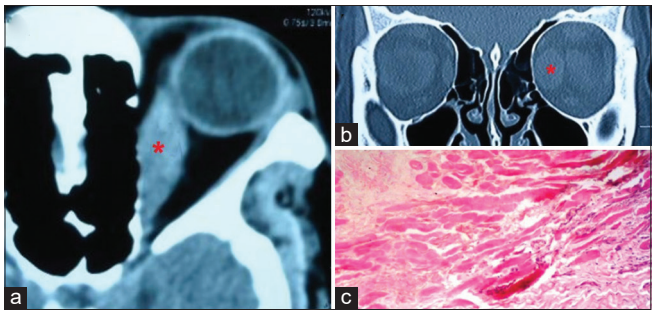


**Figure 2:** Nonspecific myositis with fibrotic changes: (a) Axial scan of CT orbit showing diffuse medial rectus muscle enlargement*, (b) Coronal scan of CT orbit showing medial rectus muscle enlargement*, (c) A muscle biopsy from the medial rectus muscle stained with hematoxylin and eosin showing sclerosing inflammation. CT = Computed tomography

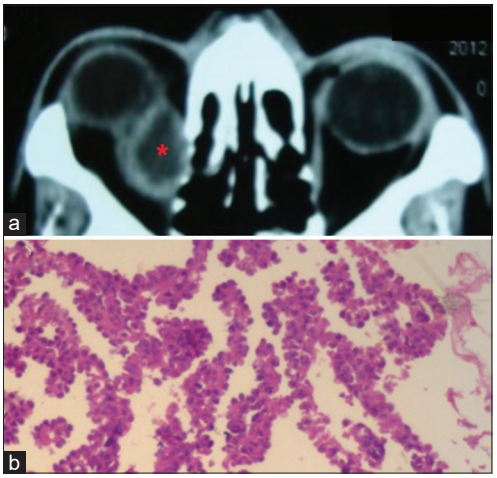


**Figure 3:** Metastasis from renal cell carcinoma: (a) Coronal scan of CT orbit showing nodular medial rectus muscle enlargement*, (b) A muscle biopsy from the medial rectus muscle stained with hematoxylin and eosin showing invasion by malignant cells of metastasizing renal cell carcinoma. CT = Computed tomography

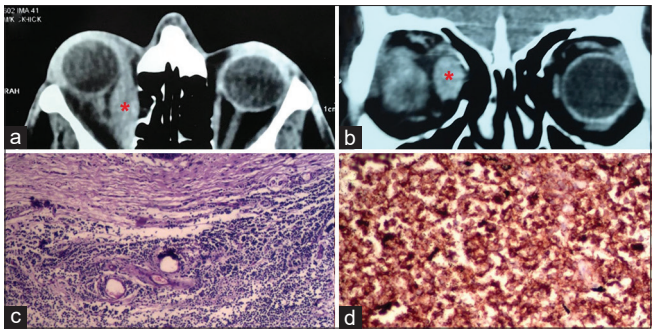

**Figure 4:** Non-Hodgkin B-cell lymphoma: (a) Axial scan of CT orbit showing diffuse medial rectus muscle enlargement*, (b) Coronal scan of CT orbit showing medial rectus muscle enlargement*, (c) A muscle biopsy from the medial rectus muscle stained with hematoxylin and eosin showing infiltration by malignant cells of non-Hodgkin lymphoma, (d) Strongly positive CD20 immunohistochemical staining. CT = Computed tomography

Paraneoplastic syndromes may accompany malignancies and result from nonmetastatic affliction of different organ systems, including the orbit and EOMs.[36] The pathogenesis is not well understood. One proposed mechanism is the development of antibodies formed against tumor cells, that cross-react with antigens of normal tissues including EOMs, which may cause inflammation, enlargement, and destruction. Occasionally, these findings occur prior to primary tumor diagnosis, so it is important if suspected, to perform a systemic survey and possible muscle biopsy to differentiate between paraneoplastic syndrome and other causes of EOM enlargement.[8,36]

### *Vascular disease*

Several vascular diseases affect the EOMs, but one of the most common is the carotid-cavernous fistula. This arteriovenous shunt can cause a retrograde flow of blood leading to superior ophthalmic vein and EOM engorgement. Edema and subsequent uniform rectus muscle enlargement occur unilaterally (although bilateral cases have been described). Less commonly, enlarged EOMs may occur secondary to congenital orbital vascular malformations, in which a spontaneous intramuscular hemorrhage has been reported.[9]

### *Amyloid*

Amyloidosis occurs as a derangement in which an abnormal amorphous hyaline material is accumulated extracellularly.[37] Amyloidosis can involve the EOMs secondary to a systemic disease, such as rheumatoid arthritis and plasmacytoma, called secondary amyloidosis, or it can involve the EOMs primarily with no underlying systemic disorder, called primary localized amyloidosis.[37]

Amyloidosis may involve a range of periocular tissues, including the eyelid, conjunctiva, lacrimal gland, and EOMs, preferentially the inferior rectus muscle.[38] Histologically, amyloid material is seen as an extracellular eosinophilic material with birefringence under polarized light and Congo red staining.[39] It should be noted that nodularity may be seen in some cases of amyloidosis.[37]

### *Hormonal disorders*

Acromegaly is a disease that occurs secondary to oversecretion of the growth hormone (GH) usually due to pituitary tumors. The abnormal hypersecretion induces organomegaly of different body organs, including the EOMs. Clinically, patients present with a diffuse symmetrical enlargement of the EOMs producing mild limitation of the ocular motility and proptosis. Usually, these findings are more dependent on the duration of the disease rather than the level of circulating GH.[40]

Congenital thyroid eye disease that occurs secondary to the antithyroid antibodies transmitted from a mother with dysthyroid condition via the placenta may be the cause of congenital enlargement of EOMs. However, this congenital enlargement is rarely encountered and very little is known regarding the actual cause and the patient presentation, it may be idiopathic or part of congenital orbital fibrosis.[41,42]

### *Drug induced*

Some patients with bipolar disorder treated with *lithium carbonate* may develop bilateral enlargement of the EOMs. This enlargement typically resolves with cessation of this medication. It has been proposed that lithium might act as a cross-reactive hapten forming thyroid autoantigens and thus inducing a Graves-like autoimmune process seen in thyroid eye disease.[9]

## According to the extent of involvement

A. Multiple muscle enlargement, involving the inferior and the medial rectus muscles, in addition to the superior rectus and levator palpebrae superioris muscles, should alert the clinician to the likelihood of thyroid eye disease[43]
B. Nodular enlargement of EOMs together with orbital fat involvement may suggest a secondary infiltrative neoplasm from the adjacent adnexa or paranasal sinuses[44]
C. Enlargement of the superior rectus together with the lateral rectus suggests spread from infection, inflammation, or neoplasia of the lacrimal gland. If enlargement simultaneously involves the inferior and lateral rectus muscles, this suggests infiltration from a sphenoid wing meningioma[45]
D. Inferior rectus muscle enlargement associated with enlarged infraorbital nerves and sinus involvement suggests IgG4-related orbital disease[46]
E. Enlarged EOMs associated with widening of the superior orbital fissure suggest neurofibromatosis[9]
F. Nodular or diffuse involvement of the lateral rectus

should suggest a possible lacrimal gland tumor because of the shared blood supply from the lacrimal artery. This enlargement may also occur secondary to leukemia because of high bone marrow density in the nearby zygomatic and sphenoid bones.[47]

### According to clinical features

A. Painful limited ocular motility (either active movement or with forced duction) with focal injection over muscle insertion, with a good initial response to corticosteroids, suggests idiopathic orbital inflammatory disorder (IOID). Examination of EOMs should provide some clue as to clinical diagnosis. Thyroid eye disease (TED) shows restriction in the opposite field of action due to muscle infiltration, whereas IOID patients may have limited movement in the field of muscle action[48]
B. A painless palpable mass emanating from the muscle with an acute onset and a slowly progressive course may alert the clinician to a possible neoplastic lesion[8]
C. Restrictive ocular motility suggests thyroid eye disease, metastasis (especially scirrhous breast carcinoma), and other fibrotic disorders[43]
D. Diffusely engorged nontender episcleral and conjunctival vessels with pulsatile proptosis and an audible bruit are suggestive of carotid-cavernous fistula, while inducible proptosis with Valsalva maneuver is suggestive of distensible venous malformation.[9]

## Diagnosis of the Extraocular Muscle Enlargement

Diagnosis of EOM enlargement depends on history, clinical examination, imaging, and laboratory testing, and muscle biopsy.

### Imaging

EOMs can be imaged by various modalities including computed tomography scan (CT scan), magnetic resonance imaging (MRI), and ultrasonography (US). CT demonstrates some EOM pathologies but is best for the bony orbit rather than soft tissues. MRI is the best modality to demonstrate the features of the EOMs and orbital soft tissues. US can reveal the reflected echogenicity of the orbital tissues to give a general idea of their nature.[9]

#### *Parameters that are assessed in the extraocular muscles on orbital imaging*

##### The shape of extraocular muscles

The enlargement of the EOMs may be focal or diffuse and also with or without muscle tendon involvement. Tendon sparing mostly occurs in thyroid eye disease, but it is not pathognomonic as there are reported cases of thyroid eye disease with tendon involvement. Tendon involvement usually occurs in cases of myositis and less commonly in lymphoma.[49] Diffuse enlargement usually indicates a vascular or inflammatory disorder while focal or nodular enlargement is usually suggestive of a neoplastic lesion.[9]

##### The size of the muscle

Normally muscle diameter measured on CT is 4.1 mm ± 0.5 mm, 4.9 mm ± 0.8 mm, 3.8 mm ± 0.7 mm, and 2.4 mm ± 1.4 mm for the medial, inferior, superior, and lateral rectus muscles, respectively.[9] In most pathological conditions involving the EOMs, enlargement is noted, except in some fibrotic cases such as sclerosing inflammation and metastasis from scirrhous breast or gastric carcinoma.[50]

##### The pattern of muscle involvement

Muscle enlargement may occur in a single muscle, in multiple muscles, or in muscle-plus disease in which muscle is involved in addition to other orbital tissues such as the lacrimal gland.[51] Single-muscle involvement is more common in neoplastic conditions while multiple muscle involvement is more common in thyroid eye disease and orbital myositis. Unilateral involvement is more common in neoplastic and arteriovenous shunt disorders while bilateral affection is more common in thyroid eye disease and orbital myositis.[52]

##### Signal intensity in magnetic resonance imaging

Normally EOMs appear dark in T1 and T2 MRI images. A hyperintense signal in T2 image indicates increased intra- and extracellular fluid, which tends to occur in cases of inflammation and neoplasm, while decreased intensity occurs in fibrotic disorders. With gadolinium contrast, an enhancement may indicate inflammation, infiltration, or venous congestion, while malignancy produces a heterogeneity.[51]

##### The structure of the muscle

Malignant lesions produce suspicious changes in the muscle structure detected on imaging. These changes include irregular edges, nodularity, and focal intramuscular mass. The presence of fat within an EOM can suggest a benign process, as new fat formation can occur in longstanding thyroid eye disease.[53] Calcifications that occur in EOMs suggest several pathological entities including orbital metastasis, longstanding orbital inflammation, meningioma, amyloidosis, and neurofibromatosis.[54]

##### The tissue echogenicity

Ultrasound is rarely utilized for diagnosis. However, low ultrasonic reflectivity suggests myositis while low-to-medium reflectivity suggests a neoplastic lesion.[55]

### Muscle biopsy

EOM biopsy is considered an important step in the diagnosis of patients with enlarged EOMs. Any delay in diagnosis affects proper treatment and the course of the disease.[51]

Some clinicians prefer a trial of systemic steroids prior to EOM biopsy. One potential side effect is not only delay in definitive diagnosis but also steroid complications and obscuration of the histopathological interpretation.[51] Patients with an atypical clinical presentation, history of malignancy, or if there are equivocal clinical and radiological findings are candidates for EOM biopsy.[51] Muscle biopsy is typically performed under general anesthesia through a conjunctival incision and localization of the muscle with the muscle hook. A specimen approximately 4 mm by 4 mm is taken from the muscle parallel to its long axis within the middle one-third of the muscle belly so as not to induce torsion. The conjunctiva is closed. The specimen is placed formalin and sent to the histopathologist.[8,51]

## Treatment of the Extraocular Muscle Enlargement

Treatment is dependent upon the cause of EOM enlargement. Specific and appropriate treatment will likely reduce the size of the muscle with subsequent improvement of the clinical signs, including diplopia. If fibrosis or muscle destruction is present, residual muscle restriction or paresis may cause persistent diplopia. EOM enlargements caused by specific infections are treated by appropriate antimicrobials. Chemotherapy and/or radiotherapy may be used for malignancy causes of muscle enlargement. Interventional vascular treatment or sclerosing therapy are used for vascular lesions causing muscle enlargement.[7,9] Biologic therapy can be used in certain diseases such as Graves' disease with teprotumumab[6] and small molecule inhibitors, such as vismodegib for advanced basal cell carcinoma.[56] The mainstay of treatment for idiopathic orbital inflammations remains steroids, either with oral or local injection of steroids. Recalcitrant cases can be treated with antimetabolites or external beam radiotherapy.[7,20]

## Conclusion

EOM enlargement has various causes with different classification schemes. Accurate diagnosis depends on clinical examination, imaging, and investigations. Proper diagnosis is mandatory for the appropriate and successful treatment.

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

### Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.


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### Conflicts of interest

The authors declare that there are no conflicts of interest in this paper.

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