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Differential diagnosis of thyroid orbitopathy — diseases mimicking the presentation or activity of thyroid orbitopathy

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Abstract

Thyroid orbitopathy (TO) is the most common cause of orbital tissue inflammation, accounting for about 60% of all orbital inflammations. The inflammatory activity and severity of TO should be diagnosed based on personal experience and according to standard diagnostic criteria. Magnetic resonance imaging (MRI) of the orbit is used not only to identify swelling and to differentiate inflammatory active from non-active TO, but also to exclude other pathologies, such as orbital tumours or vascular lesions. However, a group of diseases can mimic the clinical manifestations of TO, leading to serious diagnostic difficulties, especially when the patient has previously been diagnosed with a thyroid disorder. Diagnostic problems can be presented by cases of unilateral TO, unilateral or bilateral TO in patients with no previous or concomitant symptoms of thyroid disorders, lack of symptoms of eyelid retraction, divergent strabismus, diplopia as the only symptom of the disease, and history of increasing diplopia at the end of the day. The lack of visible efficacy of ongoing immunosuppressive treatment should also raise caution and lead to a differential diagnosis of TO. Differential diagnosis of TO and evaluation of its activity includes conditions leading to redness and/or swelling of the conjunctiva and/or eyelids, and other causes of ocular motility disorders and eye-setting disorders. In this paper, the authors review the most common diseases that can mimic TO or falsify the assessment of inflammatory activity of TO. **(Endokrynol Pol 2024; 75 (1): 1–11)**

Key words: *Graves' and Basedow's disease; thyroid orbitopathy; mimic diseases; differential diagnosis*

Introduction

Orbitopathy in the course of Graves' and Basedow's disease (thyroid orbitopathy — TO) is the most common cause of orbital tissue inflammation, accounting for about 60% of all orbital inflammation in the population aged 21–60 years and about 40% in the population older than 60 years [1].

The diagnosis of TO with the coexistence of thyroid dysfunction, the presence of antibodies to the receptor for TSH (TRAb), and bilateral but not necessarily symmetrical development of orbital symptoms is usually not difficult, and the cooperation of the endocrinologist and ophthalmologist is reduced to the assessment of the presence and differentiation of TO symptoms [2]. Diagnostic problems can be presented by cases of unilateral TO, unilateral or bilateral TO in patients with no previous or concomitant symptoms of thyroid disorders, lack of symptoms of eyelid retraction, divergent strabismus, diplopia as the only symptom of the disease, and a history of increasing diplopia at the end of the day.

The inflammatory activity and severity of TO should be diagnosed based on personal experience and according to standard diagnostic criteria. Assessment of TO inflammatory activity can be performed using the clinical activity score (CAS). Magnetic resonance imaging (MRI) is not necessary to diagnose typical cases of TO but may be necessary to assess the inflammatory activity of TO, especially in those with a so-called "posterior" course. Orbital MRI is indicated in patients with unilateral or highly asymmetric exophthalmos, suspected optic nerve neuropathy, and TO with euthyroidism, while computed tomography (CT) of the orbit is par-

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ticularly indicated before planned orbital decompression surgery [3].

MRI of the orbit is used not only to identify swelling and to differentiate inflammatory active from non-active TO, but also to exclude other pathologies, such as orbital tumours or vascular lesions. This is due to the high contrast resolution of MRI, which allows the differentiation of the signal intensity of fibrous and inflammatory tissue in fat-suppressed T2-weighted images derived from turbo-inversion recovery-magnitude (TIRM) sequences. In addition, several studies have reported the ability to quantify different signals using short-T1 immersion recovery (STIR) protocols or T2 relaxation time measurements, which allows an objective assessment of inflammation independent of muscle measurements, and it positively correlates with CAS [4].

However, a group of diseases can mimic the clinical manifestations of TO, leading to serious diagnostic difficulties, especially when the patient has previously been diagnosed with a thyroid disorder. The lack of visible efficacy of ongoing immunosuppressive treatment should also raise caution and lead to a differential diagnosis of TO.

Differential diagnosis of TO and evaluation of its activity includes conditions leading to redness and/or swelling of the conjunctiva and/or eyelids, other causes of ocular motility disorders, and eye-setting disorders [5–7] (Tab. 1).

Table 1. *Diseases that need to be differentially diagnosed with thyroid orbitopathy (TO)*

1. Redness and/or swelling of the conjunctiva and/or eyelids	Dry eye disease
	Inflammation of the eyelid margins
	Allergic conjunctivitis or blepharitis
	Carotid artery fistula into the cavernous sinus,
	Eagle syndrome
2. Eye movement disorders	Isolated orbital myositis
	Myasthenia gravis muscular weakness
	Oculomotor paresis/palsy
	Lymphoma
	IgG4-related disease (IgG4-RD)
	Intramuscular tumours
	Eagle syndrome
3. Eye seating disorders	Orbital inflammations including idiopathic orbital inflammation (orbital pseudotumor)
	Primary and secondary orbital tumours
	Vascular malformations: cavernous haemangioma (single venous-lymphatic malformation surrounded by a capsule) Lymphangioma (venous-lymphatic malformation)
	Fistula of the carotid artery into the cavernous sinus
	Dacryoadenitis (idiopathic orbital inflammation (IOI), lymphoma, Wegener granulomatosis, sarcoidosis, epithelial neoplasm, IgG4-RD)
	Amyloidosis
	Eagle syndrome

Redness and/or swelling of the conjunctiva and/or eyelids

The number of patients with dry eye disease (DED) has increased dramatically in recent decades. The incidence of DED is higher in Asia than in Europe and North America, which also suggests the involvement of cultural or racial factors in its aetiology. The prevalence of DED, according to various authors, ranges from a few to as much as 35% of the population studied. Such a large difference in the results obtained, at least in part, depends on the adoption of different definitions of DED and the high variability of the populations studied [8]. The new definition of DED is as follows: "Dry eye is a multifactorial disease characterized by persistent unstable and/or deficient tear film causing discomfort and/or visual disturbances accompanied by various degrees of ocular surface epitheliopathy, inflammation, and neurosensory abnormalities". The key criteria for the diagnosis of DED are an unstable tear film, inflammation, increased tear film osmolarity, ocular discomfort, and visual disturbances [8].

TO patients often exhibit symptoms of ocular discomfort similar to those seen in DED. Dryness of the corneal surface in TO is caused by eyelid retraction, exophthalmos, lagophthalmos, restricted eye movement, as well as impaired tear gland function and changes in tear composition because of the inflammatory process of the orbit.

The most common symptoms suggesting the presence of DED include epiphora, a feeling of a foreign body or sand under the eyelids, a feeling of dryness or insufficient lubrication of the eyes, hypersensitivity to light, a sensation of eyelid heaviness, burning and fatigue in the eyes, and intermittent deterioration of visual acuity.

Diagnosis of DED involves evaluating the protective apparatus and the anterior segment of the eye under a slit lamp, measuring the tear film break time (BUT), performing the Schirmer I test, staining tests of the superficial tissues of the eye with fluorescein, Lissamine green or Bengal Rose, and assessing tear osmolarity.

In patients with an active form of TO, subjective symptoms of DED were demonstrated in 85% of subjects of the study group, and in 30% of subjects in the control group [9].

In DED, higher levels of interleukins (IL): IL-1β, IL-6, IL-8, IL-10, interferon-γ (IFN-γ), tumour necro-

sis factor alpha (TNF-α), and IL-2, and IL-17A, have been demonstrated in tears compared to controls [10]. Because of the many similarities observed between the symptoms of DED and the initial symptoms of TO with respect to the cytokine and protein markers presented, differentiating them is essential. The researchers conducted a proteomic profile analysis comparing the protein composition of tears in TO and DED. In this study, the concentrations of 18 proteins differed significantly between the study groups. Proline-rich protein 1 (PROL1), uridine diphosphate (UDP)-glucose dehydrogenase (UGDH), calgranulin A, transcription activator BRG1, annexin A1, cystatin, heat shock protein 27, and galectin were decreased in the TO group compared to the DED group. The concentration of lysozyme C was significantly higher in TO compared to DED. Thus, the tear proteome test showed a different panel of proteins in patients with TO and those with DED, which is potentially useful for screening and differential diagnosis [10, 11].

The term blepharitis is used to describe a group of inflammatory conditions involving the eyelid margin along with glands that have an outflow at the eyelid margin. Inflammation can affect all 3 anatomical structures of the eyelid, i.e., the skin, the eyelid conjunctiva, and the eyelid margin. The Meibomian glands opening near the posterior edge of the eyelid and the Zeiss sebaceous glands and Moll's sweat glands opening into the hair follicles of the eyelashes. Blepharitis can be acute or chronic, with chronic being the more common form. It usually manifests with recurrent symptoms that can change over time and involve both eyes [12]. Examination of the anterior eyelid margin shows hyperaemia, dilation of blood vessels (telangiectasias), and swelling and redness of the eyelids. Secondary lesions often caused by a hypersensitivity reaction to staphylococcal exotoxins include papillary conjunctivitis, marginal keratitis, and dry eye syndrome. There may be blockage of the meibomian gland openings with small, yellow-coloured fatty plugs within, even in patients without complaints, and swelling of the eyelids. Blepharitis is a chronic condition with episodes of exacerbation and remission. Although it is most often diagnosed in middle-aged people, the most common age of onset of the disease is in childhood [13].

Allergic conjunctivitis is a disease caused by a reaction of the eyes to environmental allergens. It is a common condition, affecting 10–20% of the population [14]. Allergic conjunctivitis is a subtype of non-infectious conjunctivitis and manifests as acute, intermittent or chronic inflammation, which is most often induced by airborne allergens. Allergic conjunctivitis is a consequence of a type 1 allergic reaction. In sensitized individuals, when an allergen reaches the conjunctiva, Th2 cells produce cytokines that induce the production of immunoglobulin E (IgE) by B cells. The main clinical symptom is chemosis, and patients usually complain of itching. The most common forms are seasonal allergic conjunctivitis (also known as hay fever), atopic conjunctivitis, spring conjunctivitis, and those associated with various ocular-mucocutaneous syndromes (atopic blepharoconjunctivitis, AKC) — the most severe form of chronic allergic conjunctivitis. AKC results from type 4 hypersensitivity, with predominant involvement of Th1 lymphocytes, which induce chemotaxis and stimulate an increase in eosinophilia. AKC is also thought to result at least in part from an IgE-dependent mechanism [15].

Early symptoms are caused by the connection between histamine and its receptors and include tearing, itching, redness, and swelling (of the conjunctiva and/or eyelids). The latter symptoms occur a few hours later and are characterized by epithelial infiltration by lymphocytes, neutrophils, basophils, and eosinophils. This later phase leads to chronic inflammation, manifested by photophobia, eye pain, visual disturbances, and serous secretions [16].

Eagle's syndrome is a rare and poorly understood condition characterized by an elongated styloid process or calcified stylohyoid ligament. An elongated styloid process can be found in 4–7.3% of the population [17]. The most common symptoms of the syndrome are neck pain, dysphagia, foreign body sensation in the throat, otalgia, pain when yawning, or pain when turning the head. Another important group of symptoms are vascular symptoms related to carotid artery compression, such as transient ischaemic attacks and even cases of ischaemic stroke, and ocular symptoms such as Horner's syndrome, ischaemic neuropathy, or double vision [18]. In addition, an elongated corneal process can compress the jugular vein in certain head positions, causing reduced venous outflow with symptoms of periorbital tissue oedema, and venous stasis in the conjunctival and retinal vessels that mimic TO symptoms [7].

Eye movement disorders

Isolated orbital myositis is one of the locations of idiopathic orbital inflammation (IOI), previously known as orbital pseudotumor. Isolated orbital myositis was originally thought to be a unilateral process involving a single muscle, especially in the initial phase of inflammation, but it has been shown that this inflammation often involves more than one muscle and is often bilateral [19].

Extraocular muscles differ from skeletal muscles in having a smaller motor unit size, higher blood flow,

and a higher volume of mitochondrial fraction, which allows inflammatory cells to reach the muscle more easily, causing inflammation.

Typical clinical signs include orbital discomfort, moderate to severe pain in the orbit or periorbital area, painful double vision increasing with eye movements, exophthalmos, swollen eyelids, conjunctival congestion, or chemosis [20, 21]. The muscle most affected by inflammation is the medial rectus muscle, followed by the superior rectus muscle, lateral rectus muscle, and inferior rectus muscle, in contrast to TO in which inflammatory lesions usually affect the inferior rectus muscle [22]. The diagnosis is made on the basis of clinical findings, medical history, laboratory tests, and imaging examinations (MRI), which are helpful in excluding diseases with a similar clinical picture.

The most common image on MRI is poorly demarcated, tumour-like, enhancing soft tissue involving any area of the orbit. The examination can show extraocular muscle inflammation with tendon involvement, orbital fat inflammation, inflammation and enlargement of the lacrimal glands (dacryoadenitis), involvement of the optic choroid complex, the choroid membrane, and sclera, and even diffuse orbital involvement [23].

Because the diagnosis of IOI is a diagnosis by exclusion, a physical examination and clinical history are essential to rule out associated diseases, including systemic immune diseases such as orbital cellulitis, optic neuritis, TO, sarcoidosis, histiocytosis, Wegener's granulomatosis, Tolosa-Hunt syndrome, optic nerve gliomas, lymphomas, and other malignancies. Infection is a common cause of IOI, which can be hidden in surrounding orbital structures [24, 25].

Currently, the first-line treatment for isolated orbital myositis comprises corticosteroids as well as targeted radiotherapy, antimetabolites, immunosuppressants, and surgical removal of the tumour [26]. Prednisone at a dose of 1 mg/kg/day for one week is recommended, followed by a dose reduction for 6 to 12 weeks. In very severe cases, intravenous methylprednisolone can be given at a dose of 0.5–1.0 g for 3 days, followed by a switch to the previously mentioned regimen and a slow reduction of the dose. If there is a recurrence, the dose should be increased again by 5–10 mg of prednisone per day for a week until symptoms resolve [26].

Myasthenia gravis (MG) is a rare autoimmune disease characterized by autoantibodies that inhibit the normal function of acetylcholine receptors in the postsynaptic membrane of the neuromuscular junction. MG is a clinically heterogeneous disease that can manifest as skeletal muscle weakness and/or fatigue. The most common form of the disease, referred to as ocular MG (OMG), is isolated involvement of the upper eyelid lever muscle and/or extraocular muscles, which clinically manifests as blepharoptosis and/or diplopia [27, 28]. Aguirre et al. showed that the average age of onset of MG was 38 years, and 30% had MG of late onset (age of onset > 50 years). In most patients, the disease started with the ocular form (52%). MG associated with thymoma accounted for 11.6% of cases. 27.1% had other autoimmune comorbidities, the most common of which was autoimmune thyroid disease (81.2%) [29, 30].

The diagnosis of MG is confirmed by the presence of antibodies to the acetylcholine receptor (AChR-ab) and antibodies to muscle-specific tyrosine kinase (MuSK-ab) in the serum. In patients with negative serological tests, the diagnosis is based on neurophysiological findings — decreased response to repetitive low-frequency nerve stimulation (RNS) or increased oscillations in single-fibre electromyography [28, 31]. Diagnostic criteria according to the Myasthenia Gravis Association of America, 2015, consider the presence of eyelid drooping symptom and/or double vision at the onset of the disease sufficient to establish a diagnosis of OMG [32].

Paresis/paralysis of the oculomotor muscles: the nerves innervating the extraocular muscles include the oculomotor nerve (III cranial nerve), which innervates all extraocular muscles except the lateral rectus muscle (VI cranial nerve) and the superior oblique muscle (IV cranial nerve). Oculomotor nerve paresis (III cranial nerve) is a common neurological disorder. The most common causes of its damage are vascular lesions in the course of diabetes and hypertension, demyelinating diseases, primary and metastatic brain tumours, cerebral aneurysms and haematomas, head trauma, pituitary stroke, and vasculitis in the course of systemic diseases [33]. Symptoms of oculomotor nerve lesions include strabismus consistent with the extent of its innervation, as well as diplopia. Clinical signs are typical. It is necessary to search for the cause of the damage, imaging examination of the head and orbit, and neurological examination [33].

IgG4-related disease (IgG4-RD) is a recently described chronic immune-mediated disease characterized by involvement of multiple organs with the presence of tumour-like masses of a fibrotic nature, most commonly affecting the pancreas, bile ducts, lacrimal glands, orbital tissues, salivary glands, lungs, kidneys, retroperitoneal tissues, aorta, meninges, and thyroid gland [6]. The disease is characterized by high serum IgG4 levels, an elevated IgG4/IgG ratio (> 40%), and tissue infiltration by IgG4-positive plasma cells, accompanied by polyclonal hypergammaglobulinaemia. Serum IgG4 levels and oligoclonal plasmablasts are the 2 main diagnostic and prognostic biomarkers [34, 35]. The most accurate data on the prevalence of IgG4-RD comes from

Japan, where its incidence was estimated at 0.28–1.08 cases per 100,000 persons [36].

Four clinical phenotypes of IgG4-RD have been distinguished: pancreatobiliary, retroperitoneal (aortitis), head and neck confined, and Mikulicz disease (systemic). IgG4-related orbital disease (IgG4-ROD) is a condition that can represent a significant proportion of idiopathic lymphoplasmocytic or sclerotic orbital lesions previously referred to as pseudotumours. Orbital involvement in IgG4-RD is quite common, and the orbit was the first extra-pancreatic site to be reported. It can involve the eyelid, lacrimal gland, extraocular muscles, orbital soft tissues, orbital nerves, and the nasolacrimal duct, giving symptoms of eye motility disorders, diplopia, congestion, and exophthalmos [37, 38]. The lacrimal gland is the most common site of orbital lesions in IgG4-ROD [39]. Simultaneous involvement of 2 pairs of lacrimal, submandibular or parotid glands is known as Mikulicz disease [38]. IgG4-RD is considered a systemic disease, and orbital cases are often associated with extraocular disease.

Silent sinus syndrome (SSS), or imploding antrum syndrome, is a very rare condition, usually involving asymptomatic spontaneous collapse of the sinus walls and orbital floor. It arises as a result of hypoventilation of the maxillary sinus following obstruction of the osteomeatal complex, i.e., the area below the middle nasal auricle with the opening of the maxillary, frontal, and sieve sinuses. This process leads to chronic inflammation with maxillary sinus atelectasis, demineralization of the orbital floor bone, and subsequent collapse [40]. Enophthalmos occurs in 98–100% of cases; hypoglobus is less common and occurs in only 53% of patients. In 90% of patients, retraction of the upper eyelid and pseudo-Graefe's sign can be observed, and double vision is common [41].

Eye-setting abnormalities (unilateral or bilateral exophthalmos)

Many inflammatory conditions of the orbital tissues can mimic TO, requiring careful evaluation to make a proper differential diagnosis. Most of these conditions are immunologically based. Most of them are mild, but they can be quite severe, and some can result in vision impairment. The most common inflammatory condition affecting the orbital tissues and mimicking TO is idiopathic orbital inflammation (IOI). Other, rarer orbital diseases that should be considered in the differential diagnosis of TO include infections, orbital manifestations of systemic diseases, primary and secondary orbital neoplasms, and orbital vascular lesions. In most cases, when orbitopathy occurs in the absence of hyperthyroidism, the diagnosis of the disease causing the ocular symptoms is based on the exclusion of other conditions [1].

Idiopathic orbital inflammation (IOI), formerly known as orbital pseudotumour, is a benign, non-infectious inflammation of the orbit. The cause of IOI is unknown. It is usually unilateral and accounts for about 8–20% of all massive orbital lesions. Depending on the location in the orbit, it can be distinguished between anterior inflammation, diffuse inflammation, posterior inflammation, isolated myositis, or inflammation of the lacrimal glands [42, 43]. The course of the disease can be acute, recurrent, or chronic. Pain, "red eye" syndrome, double vision, and/or decreased visual acuity are typical for the acute phase. In the chronic course, exophthalmos persists without accompanying additional symptoms, which can lead to significant eye motility disorders with eyelid drooping and deterioration of visual acuity. Depending on its location, IOI can exhibit a variety of clinical manifestations. Inflammation located in the anterior part of the orbit involves the eye, conjunctiva, eyelids, nerves, and adjacent muscle structures, most often resulting in periorbital pain and swelling. Other symptoms include conjunctival chemosis and limited mobility of the eyeball, and rarely exophthalmos. Patients with diffuse IOI have symptoms similar to those of anterior IOI but more severe, and exophthalmos is more common compared to anterior IOI [44]. Posterior (involving the orbital apex) IOI occurs with orbital pain and reduced eye movement, often with visual disturbances, but with slight proptosis. Inflammatory lesions in the orbital apex can spread intracranially through the superior orbital fissure, the optic canal, and the inferior orbital fissure [45, 46].

Dacryoadenitis (tear gland inflammation) is the most common subtype of IOI, accounting for about 50% of all IOI cases [47]. The typical acute course of dacryoadenitis includes a painful, hard, erythematous mass with swelling of the lateral upper eyelid and S-shaped eyelid drooping, sometimes associated with dry eye. In 20% of patients, both lacrimal glands are involved, either simultaneously or alternately [47]. Since the description of IgG4-related disease, the subgroup of patients with an initial diagnosis of idiopathic dacryoadenitis has been revised and partially reclassified as IgG4-related dacryoadenitis [6].

The diagnosis is a diagnosis by exclusion of other causes based on imaging examinations, fine-needle biopsy, or surgical biopsy [48]. This approach helps distinguish inflammatory orbital pseudotumour from other orbital diseases. When the clinical and radiological picture of an orbital inflammatory tumour is inconclusive, a pathological examination of the tissue biopsy – obtained using a minimally invasive method and under local anaesthesia – is recommended to most effectively establish the diagnosis. For other types, such as myositis and apical IOI, where surgery is difficult or

dangerous, orbital biopsy is not considered first [49]. A good response to corticosteroids can be seen in most orbital diseases with a lymphocytic component of the infiltration [42].

Orbital tumours are divided into primary tumours arising from orbital tissues, tumours penetrating the orbital cavity from surrounding tissues, and metastases from other parts of the body. The main symptom is exophthalmos, reduction of eye movement with or without double vision, swelling and redness of the eyelids, and conjunctiva [50, 51].

Primary orbital tumours

According to the American Cancer Society, the incidence of orbital tumours is less than one per 100,000 persons [52]. The symptomatology of developing orbital tumours is initially quite sparse because surrounding tissues adapt to the slowly growing tumour, delaying the final diagnosis [50]. When the tumour reaches about 1 cm in diameter, it begins to push out the eyeball, and the patient has a vague feeling of tension and tightness in the orbit. As the tumour enlarges, exophthalmos occurs, along with restricted eye movements and dysopsia. Tumours located in the orbital cone cause relatively rapidly increasing exophthalmos, with a decrease in eye movement and early fundus changes and dysopsia [50, 52]. In a retrospective study, Markowski et al. showed that the most common symptoms in patients with primary orbital tumours were exophthalmos (by at least 2 mm), which occurred in 100% of patients, restriction of eye movement in 45%, dysopsia (diplopia in 16%) impaired visual acuity occurred in 43%, eye pain in 30%, swelling and redness of the conjunctiva and eyelids in 54%, headaches in 26%, blindness in 6%, and blepharophimosis in 51% [52]. In the study group, malignant tumours were observed in 45.9% of patients, while benign tumours were diagnosed in 34.4%, and inflammatory tumours in 15.6% of patients. The most common orbital tumour was IOI (pseudotumour) (14.75% of patients). Malignant lymphoma was detected in 11.47% of patients. According to the authors, the most common primary malignant orbital tumour is Lymphoma malignum followed by melanoma malignum, carcinoma anaplasticum, carcinoma planoepitheliale, adenocarcinoma, and tumour mixtus malignus. Malignant lymphoma was detected in 11.47% of patients [51].

The group of benign orbital tumours includes tumour mixtus, haemangioma, meningioma meningioma meningotheliale, neurinoma and glioma nervi optici, neurofibromata, lipoma, fibroma, and osteoma. According to the authors, the most common benign tumour is haemangioma followed by tumour mixtus and meningioma meningioma meningotheliale [50, 51].

Benign lesions

Optic nerve meningioma is most common in women between the ages of 30–50 years and is usually unilateral, but it can occur bilaterally, especially in those with type II neurofibromatosis. The meningioma arises from arachnoid capillary cells located around the intraorbital or intracanalicular part of the optic nerve. The clinical presentation of optic nerve meningioma consists of painless gradual loss of vision and exophthalmos mimicking TO [5]. In the eye affected by the disease process, visual disturbances such as transient loss of vision, which persists for only a few seconds, are common, while others develop a defect in a part of the visual field. Later, neuropathy of the optic nerve occurs, and exophthalmos and paralytic strabismus appear [53].

MRI examination visualizes the surrounding optic nerve tumour lesion, which undergoes homogeneous contrast enhancement. The optic nerve may be located in the centre or peripheral to the lesion. Occasionally, abnormal hyperintense optic nerve signal is observed in T2-dependent images, most likely as a consequence of chronic venous insufficiency [54]. The distinguishing mark between optic nerve meningioma and optic nerve glioma is the dilation of the optic nerve by the glioma. Orbital lymphoma can sometimes surround the optic nerve, mimicking optic nerve meningioma on imaging examinations. The tendency of lymphoma to conform to the shape of infiltrated structures makes it easier to distinguish from meningioma, which usually deforms surrounding structures [55]. The clinical manifestations of meningiomas depend on the location of the tumour. Early diagnosis is important because complete removal of the tumour may be possible, and the patient may preserve normal vision. Neurosurgical treatment and craniotomy with tumour resection comprise the treatment of choice [5].

Cavernous vein malformations (CVM), formerly called orbital cavernous haemangiomas (OCH), are the most common orbital vascular lesions in adults, and they usually occur in the fourth and fifth decades of life. According to the International Society of Vascular Anomalies - International Society of Vascular Anomalies (ISSVA), CVM are classified as low-flow venous malformations that do not distend [55]. They can affect intraorbital or adjacent structures and are considered "anatomically" malignant.

It is a benign lesion, usually single and unilateral, characterized by a well-formed capsule and numerous large vascular canals. The most common symptom of CVM is progressive axial exophthalmos. There may be optic nerve damage with varying degrees of visual

impairment. Clarós et al. in a study of 76 patients with CVM showed unilateral proptosis in all of them, while vision loss was found in 42.1%. On ophthalmologic examination, lagophthalmos was present in 76.3%, blepharoptosis in 21.1%, corneal complications in 19.6%, strabismus in 13.2%, and fundoscopic abnormalities in 60.5% [56].

The course of CVM can be different: some remain stable for several years, while others increase more rapidly; however, spontaneous orbital haemorrhage secondary to CVM rupture is very rare [57].

CT and MRI imaging is particularly important in the diagnosis of patients with orbital vascular disorders. Improved CT and MRI imaging, along with dynamic CT angiography, MRI angiography, MRI venography, and multiphase dynamic contrast CT/MRI imaging, has proven beneficial in identifying as well as differentiating various orbital vascular lesions [58, 59].

Surgical treatment is usually required for symptoms of optic nerve compression and/or for large asymmetric exophthalmos [60]. Orbitotomy represents the traditional surgical approach. With the evolution of minimally invasive techniques, endoscopic methods have gradually gained importance in the treatment of orbital lesions as well. The endoscopic endonasal route has been widely adopted for lesions involving the medial and inferior orbit with excellent results [61]. More recently, transorbital neuroendoscopic surgery (TONES) has become a possible option for the safe treatment of several lesions in the upper-lateral orbital compartment [62].

Dural arteriovenous fistula (DAVF) in the cavernous sinus (CS) (carotid-cavernous fistula [CCF]) is a form of abnormal arteriovenous communication that can be treated with endovascular embolization [63]. Liu et al., using digital subtractive angiography, showed that 34.4% of DAVFs were unilateral, and 82.8% were perfused by both the external carotid artery and internal carotid artery [64].

CCFs can occur spontaneously or after trauma and are caused by damage to the cavum wall of the internal carotid artery or one of its small branches. Most traumatic CCFs are associated with head trauma, and very few occur after a cranial base fracture [65].

Barrow et al. classified CCF into 4 subtypes based on fistula communication. Type A CCF are direct high-flow connections between the internal carotid artery and cavernous sinus. Young men are at the greatest risk because the main cause is head trauma. Symptoms are sudden, and headaches and murmurs (subjective or auscultatory) are common. B-D type CCF are low-flow indirect connections; risk factors include atherosclerosis, hypertension, diabetes, and collagenosis and are more common in postmenopausal women [66]. Unlike direct CCF, they usually do not have a murmur and have a more insidious onset and may close spontaneously. Direct CCF have a risk of progression and mortality without being closed [66].

Patients with CCF may have different ocular complaints depending on the type and severity of the vascular abnormality. They may present with typical clinical features that lead directly to the diagnosis, or subtle and nonspecific symptoms that cause delay or misdiagnosis. Direct CCF often manifests with an orbital murmur, proptosis, retrobulbar nerve palsy and conjunctival hyperaemia (the most common symptom), and venous stasis retinopathy mimicking TO symptoms [67]. Patients may also have ocular paresis without stasis symptoms when arterial blood is sent back to the superior cuneiform sinus or inferior cuneiform sinus [63]. According to Liu et al., the most common symptoms are exophthalmos (39.1%), chemosis (35.9%), and headache (28.1%) [64].

Diagnosis is based on angio CT, angio MRI, and digital subtractive angiography (DSA) to clarify the size and location of fistulas [63, 68, 69].

Amyloidosis is a storage disorder that can be local or systemic, primary or secondary to chronic inflammatory diseases. Orbital involvement is more common in the primary form of amyloidosis [70, 71]. Amyloid is an extracellular, protein-like material that can be deposited in various tissues. Histopathological identification is preferably performed by Congo Red staining. When viewed under a polarizing microscope, all forms of amyloid show green birefringence. The clinical classification includes the following: 1. primary generalized amyloidosis (without any underlying disease); 2. secondary amyloidosis (associated with chronic infection or rheumatoid arthritis); 3. amyloidosis associated with myelomatosis; and 4. tumour-forming amyloidosis, characterized by localized amyloid masses [72]. Ocular manifestations can occur in all types of amyloidosis. The most common are amyloid tumours of the conjunctiva and eyelids, while isolated orbital amyloidosis is rare [71, 73].

Monteiro et al. presented a case of a patient with autoimmune hypothyroidism who developed unilateral exophthalmos due to enlargement of the rectus inferior muscle [73]. The patient was initially treated as TO. Given the abnormal reduction in ocular depression and the presence of calcification on imaging studies, an alternative diagnosis was considered, and the patient was subsequently diagnosed with primary isolated orbital amyloidosis. Abnormal eye movement, lack of eyelid retraction, and unilateral presentation should prompt the doctor to conduct further diagnostic tests. In TO, the inferior rectus muscle is most often involved in autoimmune inflammation with its restrictive dysfunc-

tion. As a result, patients show limitations in looking upward, but usually they do not show a deficit in turning the eye downward. The presence of a significant ocular depression deficit is an important clinical sign, suggesting the need to expand the diagnosis of TO [73].

Malignant lesions

Even when clinical signs indicate TO, clinical deterioration despite treatment of the disease should raise caution and the need for imaging studies to exclude other pathologies, such as orbital malignancy.

Orbital lymphoma is usually a B-cell non-Hodgkin's lymphoma (NHL) originating from the lymphoid tissue of the mucous membranes of the ocular adnexa [74]. It is mainly derived from the eyelids, extraocular muscles, conjunctiva, or lacrimal glands. Lymphoma arising from one of these locations is called primary orbital lymphoma (POL). Lymphoma arising from extraocular locations with metastasis to the orbit is called secondary orbital lymphoma [54, 75]. Among all orbital malignancies, 55% are lymphomas [76]. The incidence of orbital lymphoma is 1–10% of all NHL and 5–15% of all extranodal NHL. Orbital lymphoma can be seen between the ages of 15 and 70 years, but most cases occur between the ages of 50 and 70 years [76].

POL often manifests as proptosis, or a palpable mass that causes swelling of the eyelids. It can also be associated with other symptoms such as restrictions in eye movements, diplopia, and ocular pain. Visual acuity is reduced mainly due to infiltration of the optic nerve or compression caused by the effect of the mass [54].

Zhu et al., in a study group of 72 patients with histologically confirmed POL, showed that the most common clinical manifestations were eyelid swelling (n = 42), proptosis (n = 35), ocular pain (n = 25), conjunctivitis (n = 23), self-perception of mass (n = 20), visual acuity or field changes (n = 18), blepharoptosis (n = 15), and ophthalmoplegia (n = 9). In the study group, 70.8% had unilateral and 29.2% had bilateral lesions [54].

Hajduković et al. and Moura Neto et al. presented the similar rare cases of mucosa-associated lymphoid tissue lymphoma giving a view that suggests TO in patients diagnosed with autoimmune hyperthyroidism. Orbital CT scan and biopsy showed low-grade B-cell NHL from mucosa-associated lymphoid tissue in both cases. Treatment included radiotherapy and chemotherapy, with regression of the orbital lesion [77, 78].

On CT and MRI imaging, lymphoid tumours usually take on the appearance of homogeneous lobulated lesions. They conform in shape to surrounding structures and generally do not damage adjacent bone tissue [54, 74].

Treatment options for orbital lymphomas are different (surgery, radiation therapy, chemotherapy) due to different histopathologic types and localization [54, 74, 78]. Surgical treatment with total or partial resection of the tumour is usually performed in patients with an unclear preoperative diagnosis or to relieve tumour-related symptoms. However, surgical treatment alone is insufficient to achieve favourable treatment outcomes [74]. Radiation therapy is carried out with a total dose of 30–46 Gy, with a single dose of 1.8–2 Gy and 15–23 fractions. For chemotherapy, the authors suggest a CHOP or R-CHOP regimen [rituximab, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (initial name — oncovin), prednisolone], and patients receive 4–8 cycles of treatment depending on their condition. In the group of 72 patients reported by Zhu et al., 2.5% were treated with surgery alone, 13.9% with radiotherapy, 6.9% with chemotherapy, 30.6% received combined treatment of surgery and radiotherapy, 20.8% were treated with surgery and chemotherapy, and 11.1% received surgery in combination with chemotherapy and radiotherapy [54].

Rhabdomyosarcoma (RMS) is the most common mesenchymal cancer in children and adolescents, with 10% of cases occurring in the orbit. RMS should be suspected whenever children present with rapidly progressive unilateral exophthalmos. Its symptoms depend on the origin and location of the lesion. Orbital RMS accounts for 25–35% of head and neck RMS and 10–20% of all RMS [79]. Histopathological classifications of RMS include embryonal, follicular, pleomorphic, and spindle cell subtypes. The embryonal subtype is most common, the pleomorphic subtype predominates in adults, and the diagnosis of the follicular subtype in children or adults has a poor prognosis [80, 81].

Clinical manifestations of orbital RMS include unilateral proptosis usually rapidly progressing, eyeball dislocation, strabismus, eyelid swelling, eye redness, blepharoptosis, chemosis and eye mobility disorders. The acute onset and rapidly progressive nature of the disease may mimic an infectious or inflammatory aetiology such as TO [81].

CT and MRI are 2 essential imaging methods for determining the location, size, and extent of invasion and evaluating recurrence or residual lesions after treatment. MRI better visualizes the soft tissues of the orbit, giving precise localization, vascular flow characteristics, enhancement patterns, and intracranial infiltration without the risk of radiation. On MRI, the lesion is isointense relative to the extraocular muscle on T1W images. On T2W images, the lesion is usually hyperintense relative to both the extraocular muscle and intraorbital fat. MRI with diffusion-weighted imaging (DWI) sequence is the best method for detecting residual lesions and providing follow-up after chemoradiotherapy [81, 82].

Currently, a multidisciplinary approach including surgery, chemotherapy, and radiotherapy is preferred for the treatment of orbital RMS, which has improved the overall cure to about 90% [80, 81, 83].

Metastasis to the orbit

In adults, metastasis to the orbit is generally in the form of carcinomas, while in children it is in the form of sarcomas or embryonal neoplasms of the nervous system. Metastatic lesions are more often found in the anterior part of the orbit than in the posterior [84]. The most common metastases are breast, lung, and prostate cancer, melanoma, carcinoma, renal cell carcinoma, neuroblastoma, and rhabdomyosarcoma [85, 86, 87]. Among the rapidly progressive ocular symptoms are exophthalmos, diplopia, impaired vision acuity, pain, blepharoptosis, and palpable tumour [88].

Summary

Diagnostic problems of TO may be caused by cases of unilateral course of the disease, and by unilateral or bilateral course in patients without previous or concomitant symptoms of thyroid disorders.

Orbital MRI is always necessary in patients with unilateral or highly asymmetric exophthalmos, suspected optic neuropathy, and TO with euthyroidism.

The lack of apparent efficacy of ongoing immunosuppressive treatment should also raise caution and lead to initiation of a differential diagnosis of TO.

Differential diagnosis of TO and evaluation of its activity includes conditions leading to redness and/or swelling of the conjunctiva and/or eyelids, other causes of eye movement, and eye-setting disorders.

Author contributions

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Conflict of interest

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