Review Article

Thyroid eye disease: a 2017 update from the first thyroid eye clinic in Hong Kong

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Abstract

Thyroid eye disease (TED) is the most important extra-thyroidal manifestation of the most common autoimmune disease worldwide. In this review, we summarized its clinical features into 5D and its management into 8S. We also shared our past 6 years' experience of managing nearly 700 TED patients in the first thyroid eye clinic in Hong Kong.

Nomenclature of thyroid eye disease

Thyroid eye disease (TED) is also known as Graves' ophthalmopathy/orbitopathy, thyroid-associated ophthalmopathy/orbitopathy, or thyrotoxic/endocrine exophthalmos. It is the most important extrathyroidal manifestation of autoimmune thyroid diseases (AITD) including Graves' disease and Hashimoto thyroiditis. It is also the most common orbital disorder in adults worldwide and the most common cause of unilateral or bilateral axial proptosis (exophthalmos), acquired strabismus or lid retraction.[1] TED may lead to 5Ds: visual Dysfunction, Double vision, ocular Discomfort, facial Disfigurement, and significantly Decreased quality of life.[2]

Disease spectrum of thyroid eye disease

Patients with TED may not have any clinical or biochemical evidence of thyroid dysfunction or associated antibodies. They may have isolated orbital involvement known as ophthalmic Graves' disease or euthyroid Graves' ophthalmopathy, which is more common in Asian populations (up to 6% in our series).

Epidemiology of thyroid eye disease

TED tends to have a bimodal presentation during the fourth or sixth decade of life. The risk of TED is much higher in patients aged 40-60 years than younger patients. The female-to-male ratio is about 9:1 for all forms of clinical TED and drops to 3:1 for the severe form. In a cohort of 120 Caucasian patients with TED, 90% had Graves' disease, 7% had euthyroid, 3% had Hashimoto thyroiditis, and 1% had primary hypothyroidism.[3] In a multicenter study in Sweden that involved 2916 patients, 20% of hyperthyroid patients suffered from TED at diagnosis.[4] In a Danish study, approximately 5% of patients with Graves' disease developed severe TED.[5]

Chronology of thyroid eye disease

Around 4% of TED patients present more than 6 months and 19% within 6 months *before* the diagnosis of thyroid

dysfunction. About 20% of patients have concurrent ocular and endocrine features at presentation, whereas 22% and 35% develop ocular manifestations within and more than 6 months *after* being treated for thyroid dysfunction, respectively.[3] Over 80% of patients with Graves' hyperthyroidism but no ocular involvement at presentation do not develop TED after the first course (18 months) of antithyroid medications. Mild TED resolves spontaneously in most patients.[6]

Risk factors for thyroid eye disease

The reported risk factors for the development of TED in patients with AITD include male gender, older age (>50 years) at onset, smoking, use of radioactive iodine (RAI), and post-ablative hypothyroidism.[7,8] Compared with non-smokers, smokers have more severe TED, a higher recurrent rate of Graves' disease, are more likely to show progression or occurrence of TED after radioactive iodine, and less responsive to immunosuppressants or orbital radiotherapy.[9] Statin use was shown to have a 40% decreased hazard for TED in a large US cohort,[7] but another study showed possible association of statin use with risk of liver derangement for patients receiving intravenous steroids for active TED.[10]

Clinical features of thyroid eye disease

In a Caucasian cohort, typical signs of TED included eyelid retraction (90%), lid lag (50%), exophthalmos (60%), restrictive myopathy (40%), and optic nerve dysfunction (5%) [**Figure 1**]; only 5% of the cohort had all typical signs (except optic nerve dysfunction).[3] Extraocular features include lid puffiness, lid retraction, lid lag, lagophthalmos

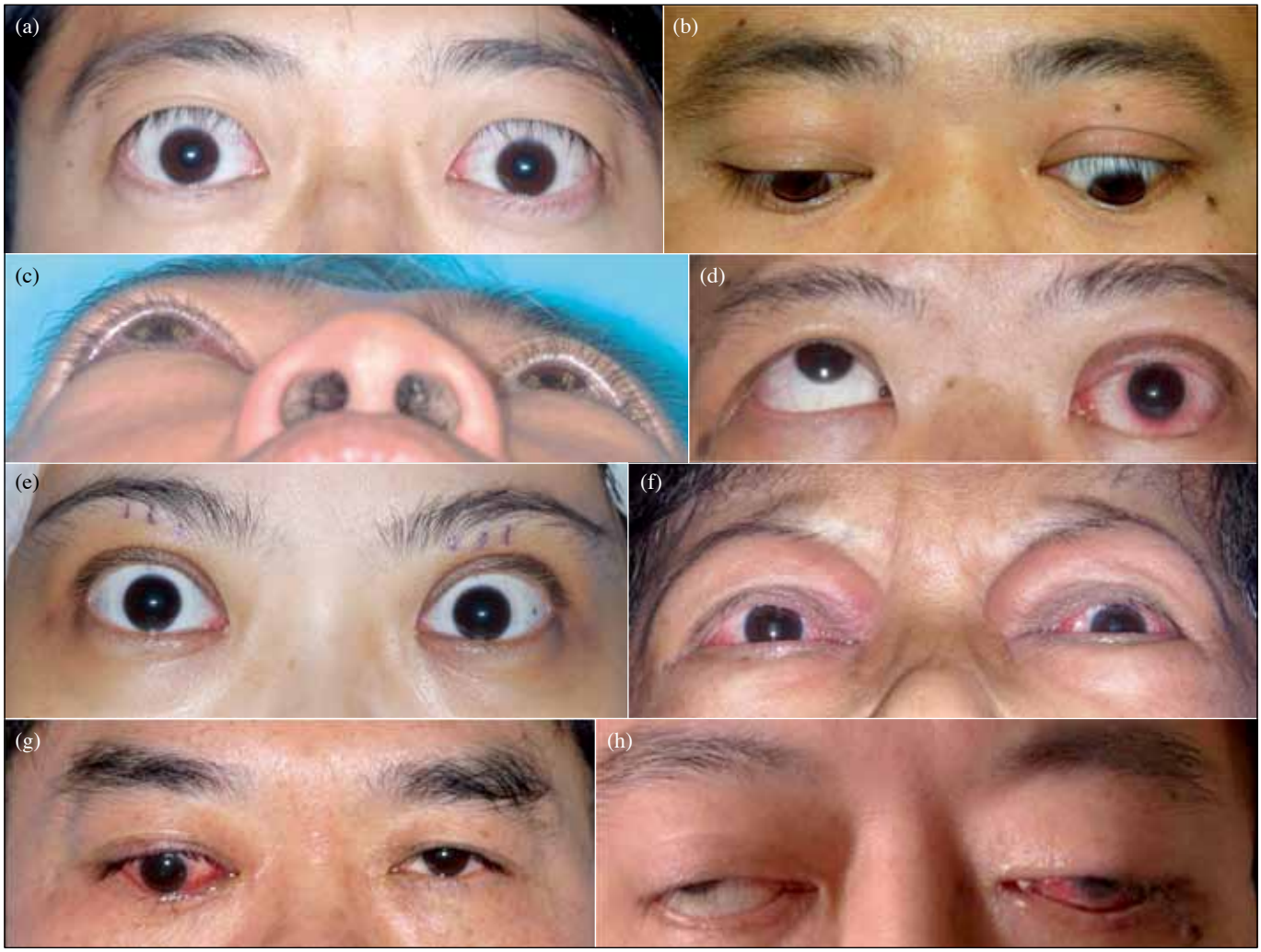

Figure 1. (a) Bilateral upper lid retraction at primary gaze, (b) left upper lid lag on downgaze, (c) asymmetric exophthalmos (more severe on the right) on worm's eye view, (d) severe restrictive myopathy affecting the left eye while attempting upgaze, (e) left dysthyroid optic neuropathy with minimal inflammatory feature or proptosis (visual acuity: right eye: 20/10, left eye: 20/70), (f) symmetric active thyroid eye disease with bilateral upper lid erythema (rare in local population), lid swelling, injection, caruncular swelling (left), chemosis and pain, (g) asymmetric active thyroid eye disease with lid edema and erythema over the right side only, and (h) bilateral lagophthalmos (incomplete eyelid closure) and poor Bell's reflex (the eyes fail to roll up upon lid closure).

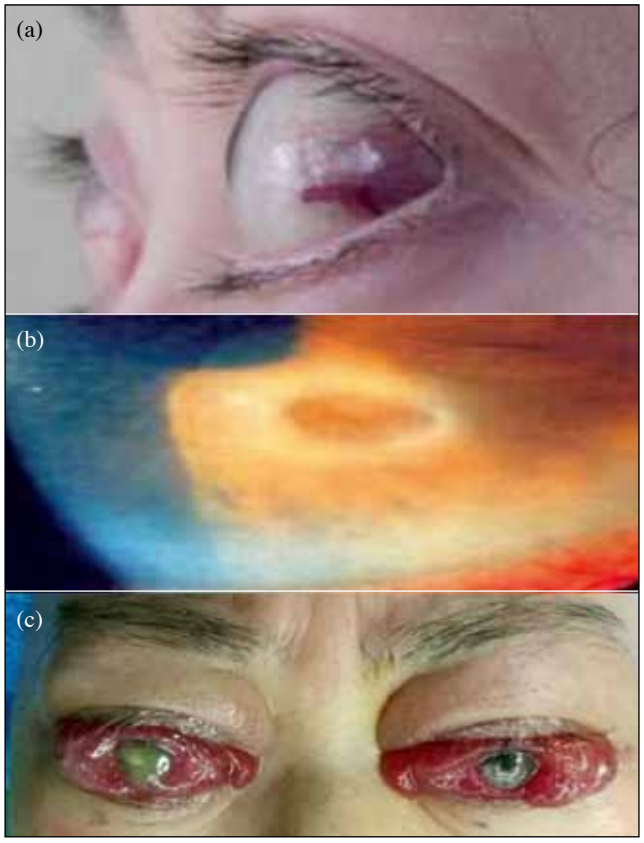

Figure 2. (a) Conjunctival injection around insertion of lateral recti muscles, (b) exposure keratopathy and early microbial keratitis, and (c) severe conjunctival chemosis, injection and bilateral microbial keratitis in a patient with active and untreated thyroid eye disease.

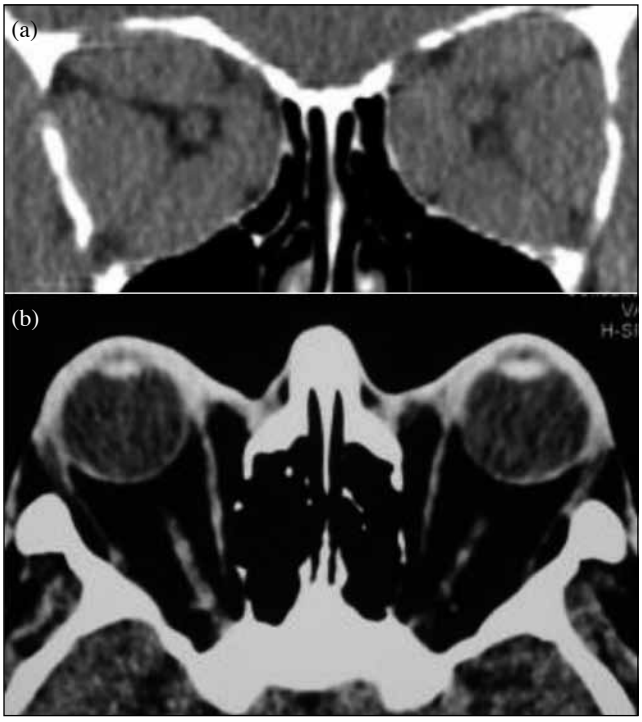

Figure 3. Coronal computed tomography of the orbits showing (a) diffuse and symmetric extraocular muscle enlargement with apical compression on the optic nerve, and (b) symmetrical severe proptosis and straightening of optic nerves with expansion of the orbital fat compartment and minimal muscle involvement in a young female non-smoker with thyroid eye disease.

(incomplete eyelid closure), axial non-pulsatile proptosis (exophthalmos), restrictive strabismus, and acquired lower lid epiblepharon in Asians (**Figure 1**). Intraocular features include conjunctival injection, particularly around the insertion of the rectus muscle, superior limbic keratitis, exposure keratopathy, chemosis, raised intraocular pressure, optic disc swelling, retinal venous congestion, and choroidal folds (**Figure 2**). Vision loss secondary to TED is related to optic nerve dysfunction (dysthyroid optic neuropathy [DON]), exposure keratopathy, uncontrolled intraocular pressure, and globe subluxation.

Proptosis (exophthalmos)

Patients with TED have axial non-pulsatile proptosis (exophthalmos) secondary to orbital venous congestion and enlargement of the extraocular muscles (EOM) due to accumulation of glycosaminoglycan and enhanced adipogenesis. Exophthalmos can be quantified using various types of exophthalmometers (e.g. Hertel) or radiologically with axial orbital scans.

Lid retraction

Lid retraction is the most common sign in TED. The normal upper lid rests at 1-2 mm below the superior limbus (corneal-scleral junction), and the lower lid rests at the inferior limbus. Differential diagnoses of lid retraction include facial paralysis, myasthenia gravis, myotonic dystrophy, Marcus Gunn jaw winking, metabolic disease (uraemia, cirrhosis), Parinaud's (dorsal midbrain) syndrome, Parkinson's disease, contralateral ptosis, and aberrant third nerve regeneration. Lid lag on downgaze, however, is not present from these other causes.

Diplopia

Diplopia or double vision is the most debilitating symptom in TED. Strabismus is restrictive (fibrotic) rather than paralytic in nature. The inferior rectus is most commonly involved, followed by the medial, superior, and lateral rectus. Movement is therefore usually worst in elevation or abduction. Radiologically, the involved EOMs are often enlarged and the tendons are frequently (not exclusively) spared. Fatty deposits within the EOM on computed tomography or T1-weighted magnetic resonance imaging are a specific feature of TED.

Dysthyroid optic neuropathy

DON is thought to be a result of optic nerve compression by the enlarged EOM at the orbital apex (**Figure 3**). In our experience, it may develop in 'cold presenters' with low clinical activity score or minimal proptosis. Postulated mechanisms of DON include inflammation, ischemia or mechanical stretching. Patients may present with horizontal

diplopia with esotropia and abduction deficits secondary to medial rectus enlargement, whereas patients with a fat predominant type of TED may have relatively normal motility but proptosis and stretching of the optic nerve is best shown on sagittal imaging (**Figure 3**). Signs of DON include reduced vision, colour vision, and visual field, presence of afferent papillary defect and optic disc swelling.[11] Patients with existing diabetes or of Asian descent (with shallow orbits) are at higher risk of developing DON. Medical decompression with the use of pulse methylprednisolone (PMP) 750 mg on alternate days x6 over 2 weeks (to avoid consecutive day high dose of 1000 mg and risk of liver dysfunction) may be considered. If response is favorable, orbital radiotherapy can be arranged shortly to prevent recurrence.[11] The rate of compressive optic neuropathy has been reported to be significantly lower in patients who received both orbital radiotherapy and steroids.[12] In our experience, DON could be resolved in selected patients who presented early with pulse steroid, radiotherapy, with or without the use of steroid-sparing agent (double or triple therapies). Nonetheless, if vision remains poor or DON recurs, surgical decompression of the medial wall and/or other walls (depending on the amount of proptosis required) should always be considered.[13]

Thyroid eye disease in Asians

Asian patients often have a delayed and atypical presentation of TED compared with Caucasians. With darker complexion, thicker skin and conjunctival tissues and possibly higher pain threshold, clinical activity score often underestimates or fails to determine deeper orbital involvement. More Asian patients with DON are 'cold-presenters'. Advanced radiological investigation may identify 'subclinical', localized inflammation and justify medical treatment for progressive deformity (e.g. proptosis and diplopia) before rehabilitative surgery. In a Singaporean cohort of 174 patients, corneal erosion secondary to acquired epiblepharon was a common sign in East Asian patients. Mean exophthalmometry values and prevalence of upper eyelid retraction and edema are comparatively lower in East Asian patients.[14]

Thyroid eye disease in paediatric patients

TED is not uncommon in the paediatric population and is usually far less severe than in adults. Among 83 Chinese children aged ≤16 years with Graves' disease, 63% had an ocular presentation: 38.6% had lower lid retraction, 13% had punctate epithelial corneal erosions, 12% had mild proptosis (<3 mm), 1.2% had limited extraocular movement, and none developed visual-threatening complications.[15] In 13 Singaporean children with TED, symptomatic acquired epiblepharon was again more common in those of East-Asian descent (69.2%).[16]

Diagnosis, grading, and investigation of thyroid eye disease

TED is graded separately by severity (tissue remodeling or deformities) and activity (inflammation). The NOSPECS grading (Normal, Only sign, Soft tissue involvement, Proptosis, Extraocular Motility, Corneal exposure, Sight-threatening) is useful to describe the combination of deformities, whereas the clinical activity score measures the degree of inflammation (erythema, swelling, tenderness, loss of function), and the recently proposed VISA (Vision, Inflammation, Strabismus, Appearance) by the International Thyroid Eye Disease Society combines both scales into one.[17]

Diagnosis of TED is still largely clinical, based on a history of autoimmune thyroid disease (Graves' disease more often than Hashimoto thyroiditis) and compatible examination findings. All patients should have appropriate endocrinological evaluation with thyroid function test for serum sensitive thyrotropin and free thyroxine and triiodothyronine levels. Thyroid-related antibodies, specifically thyrotropin receptor antibodies, may be evaluated in patients without a history of thyroid disorder. Other ancillary ocular evaluations include visual field (automated perimetry), colour vision assessment (Ishihara pseudoisochromatic plates), Hess chart (for extraocular movement), and most importantly field of binocular single vision for patients with diplopia.

Orbital imaging is helpful in patients with features of infiltrative TED (motility restriction and/or proptosis), DON, or those awaiting surgical decompression. Non-contrast axial and coronal computed tomography of the orbits readily reveals proptosis, EOM enlargement, apical compressions, and bony anatomical variants for preoperative planning. Nonetheless, it has a limited role in assessing inflammation, as EOM enlargement can be long-standing although retrobulbar fat streakiness can be seen. Diffusion-weighted magnetic resonance imaging is superior to computed tomography in differentiating acute inflammatory from chronically enlarged EOMs and in showing early EOM involvement in 'cold presenters'.[18] Signal intensity ratios on short-tau inversion recovery sequence increase with inflammatory edema and correlate positively with clinical activity score.[19] Signal intensity ratios decrease after PMP and persistently high values post-treatment are associated with treatment failure or recurrence. A prolonged T2 relaxation time is positively correlated with the degree of inflammation and can help to differentiate inflammatory from fibrotic, chronically enlarged EOM and help to identify patients in whom immunosuppressive treatment is appropriate.[20] Orbital scintigraphy, positron emission tomography computed tomography, and digital infrared thermal imaging have been used to measure disease activity with less promising results. The threshold of imaging should be low if atypical features are present.

Differential diagnoses of thyroid eye disease

Differential diagnoses of TED include other orbital disorders such as carotid-cavernous fistula, idiopathic orbital inflammation (pseudotumor), orbital or preseptal

cellulitis, and orbital tumor. Orbital imaging usually can help to differentiate these conditions, and tissue biopsy is sometimes required in patients with euthyroid Graves' ophthalmopathy.

Management of thyroid eye disease

The multidisciplinary approach in managing TED requires collaboration between physicians and ophthalmologists for early diagnosis, triaging, and referral. Treatment consists of symptomatic topical and systemic anti-inflammatory therapies as well as staged surgical rehabilitation.

The management of TED can be summarized as 8S: (1) Stabilization of thyroid function, (2) advice to avoid active and passive Smoking, (3) Staging of disease activity and severity, (4) Symptomatic treatment for dry eye and raised intraocular pressure, (5) Suppression of inflammation during active disease with steroids, radiotherapy, immunosuppressants, and biologics, (6) Staged Surgeries during the inactive phase (orbital decompression, strabismus correction, and eyelid operations), and (7) Surveillance for vision-threatening complications such as DON, severe exposure keratopathy, uncontrolled raised intraocular pressure, and globe subluxation.

Although thyroid status does not always correlate with the presence, severity, or activity of TED, early stabilisation of thyroid function is always recommended. Ophthalmologists are often consulted about the risk of using RAI in patients with Graves' disease. In different studies, up to 15 to 20% of patients who received RAI developed new-onset or worsening of pre-existing TED.[21,22] Patients who are smokers,[22] with unstable thyroid function (raised serum triiodothyronine concentration, or post-RAI uncorrected hypothyroidism) and high levels of thyroid-stimulating immunoglobulin are at risk. RAI is contraindicated in patients with active TED (clinical activity score ≥3/10), which should be managed as above first. Standard dose oral prednisolone prophylaxis (0.4-0.5 mg/kg for 3 months) can be precribed in patients with mild to moderate TED and a high risk of progression, whereas a lower dose (0.2-0.3 mg/kg for 4-6 weeks) is preferred for patients with mild TED or without preexisting TED but with risk factors. Patients without preexisting TED and risk factors do not require glucocorticoid prophylaxis.13,23 RAI presumably causes development or progression of TED by releasing intrathyroidal autoreactive lymphocytes and antigens. Subsequent hypothyroidism (even subclinical) may exacerbate TED due to accumulation of glycosaminoglycans and raised serum thyrotropin. Early and regular biochemical monitoring (every 4-8 weekly) and adequate thyroxine supplementation to prevent post-RAI hypothyroidism are crucial, particularly for those with preexisting TED.

All patients except those with the mildest form of TED benefit from topical lubricants including eye drops and gel during the daytime and thicker ointment at night with or without taping the eyelids closed. Anti-glaucomatous drops may be required to control secondary raised intraocular pressure. Sunglasses may be valuable for those with photophobia or pending surgical rehabilitation. Stick-on (Fresnel) or spectacle-incorporated prism lenses may alleviate a small to moderate degree of diplopia.

Immunosuppressants

Immunosuppressants are indicated for patients with inflammatory orbitopathy with active TED (clinical activity score ≥3/7) and can be considered for those with DON or recent-onset, progressive myopathy. Intravenous PMP has replaced oral prednisolone as the first-line treatment due to fewer side effects and higher effectiveness.[24,25] The European Group on Graves' Orbitopathy (EUGOGO) recommends intravenous 500mg PMP weekly for 6 weeks and then 250 mg for another 6 weeks in patients with moderate-to-severe and active TED.[13] In a randomized double-blind trial that compared cumulative doses of 2.25g, 4.98g, and 7.47g in 12 weekly infusions, more patients achieved improvement in TED with higher cumulative doses (28%, 35%, and 52%, respectively).[26] Nonetheless, major adverse events such as development of diabetes, depression, and severe infection were slightly more frequent in the 7.47g group.[26] Idiosyncratic hepatic failure and arrhythmia can occur at cumulative doses over 8g, although the time period over which this develops has not been specified. A single dose of PMP should not exceed 750mg and consecutive daily therapy should be avoided. Intravenous steroids are contrainidicated in patients with recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular disease or psychiatric disorders. Hypertension and diabetes should be well-controlled before starting steroids. In a review of 14 studies including 1045 TED patients, the morbidity and mortality of intravenous steroid therapy was 6.5% and 0.6%, respectively.[27] Daily oral steroid can be given alternatively for medical or social reasons. Periocular steroid injections, e.g. triamcinolone acetonide (40mg/ml), are useful for asymmetric orbitopathy, mild relapses during tapering, or when the patient is reluctant or systemic steroids are contraindicated. In patients with persistent active disease despite a full cycle of PMP, steroid-sparing agents (e.g. methotrexate, azathioprine, rapamycin, cyclosporine, cyclophosphamide) or newer biologics (e.g. rituximab,[28] adalimumab) may be considered, although high-level evidence is lacking. In a randomized controlled trial to compare rituximab with PMP in 32 patients with moderate-to-severe TED, those who received rituximab achieved a larger decrease in clinical activity score, a lower risk of disease reactivation, and better motility.[29] Nonetheless, another randomized controlled trial to compare rituximab with saline infusion in 21 patients failed to show any additional benefit from rituximab.[30,31]

Orbital radiotherapy

Orbital radiotherapy is a useful adjuvant for patients with steroid-dependent, intolerant or resistant inflammatory orbitopathy, recent-onset progressive myopathy or DON. It consists of fractionated external beam irradiation of 20Gy over ten sessions. Compared with oral steroid therapy,

orbital radiotherapy has comparable effect for moderate to severe orbitopathy and better long-term effect on motility restriction.[12] Combined intravenous PMP plus orbital radiotherapy is more effective than PMP alone.[32] The risk of DON reduces in the combined orbital radiotherapy and steroid group than in the steroid-only group.[12] Orbital radiotherapy is most useful when administered during the course of PMP but is relatively contraindicated in younger (age <30 years) patients or those with diabetic retinopathy. Complications of radiotherapy include dry eyes, cataract (especially when used with concurrent steroid), radiation retinopathy, optic neuropathy, and an increased long-term risk of malignancy.

Selenium supplementation

Selenium supplementation of 100 μg twice daily for 6 months has been shown to improve soft tissue signs and quality of life and prevent progression in patients with recent-onset mild TED.[33] Nonetheless, the study was conducted in selenium-deficient regions and supplementation is beneficial only if serum selenium level is insufficient.[34]

Surgical intervention

Except for patients with vision-threatening complications (DON, globe-subluxation, refractory exposure keratopathy), elective surgery is recommended at least 6 to 9 months after stabilization of endocrine and orbital status. An individualized, staged approach includes orbital decompression, followed by strabismus surgery, correction of lid retraction, and then blepharoplasty and other esthetic surgery.[35]

Common indications for elective orbital decompression include disfiguring proptosis, congestive orbitopathy, and medically uncontrolled exposure keratopathy or raised intraocular pressure. Orbital decompression and/or expansion are broadly classified as bone removal orbital decompression (BROD) or fat removal orbital decompression (FROD). They can be performed in isolation or in combination. BROD differs in the choice of surfaces and incisions for bone removal, e.g. medial (via transcaruncular, transcutaneous Lynch incision or endonasal transethmoidal), inferior (transconjunctival forniceal or swinging eyelid, transcutaneous subciliary or transantral), or lateral orbital walls (transcutaneous upper lid crease, lateral canthal, forniceal or coronal incision). Complications include diplopia, globe dystopia, periorbital sensory changes, orbital hemorrhage, ischemic optic neuropathy, infection, lid malposition, lacrimal gland or lacrimal drainage injury, cerebrospinal fluid leak, and rarely subarachnoid/cerebral hemorrhage.

FROD involves removing intraconal and/or extraconal orbital fat via a transcutaneous (upper lid crease or lower lid subciliary), transconjunctival, and endonasal approach. Fat pockets are usually debulked in the following sequence: inferolateral, superonasal, inferomedial, and superotemporal (to avoid the lacrimal gland and its neurovascular structures). An endoscopic medial wall approach can be used for proptosis reduction as it allows good access to the middle and posterior intraconal fat.[36] FROD may cause fewer cases of new-onset diplopia or worsening of pre-existing diplopia, compared with BROD (for a similar amount of proptosis reduction). Anecdotal experience reports improvement in motility restriction following FROD in selected cases. Orbital hemorrhage and periorbital sensory loss may develop. Very often BROD and FROD are performed in combination in either sequence depending on the surgeon's preference.

Strabismus correction in TED is challenging due to fibrotic EOM and surrounding soft tissue involvement. EOM recession instead of resection is recommended to correct the limited movement rather than the amount of ocular deviation at primary gaze. For example, bilateral asymmetric inferior rectus muscle recession is performed to correct vertical diplopia, to improve upgaze, and to avoid late progressive overcorrection. Detachment of the capsulopalpebral fascia (lower lid retractor) minimizes postoperative lower lid retraction/scleral show. Different techniques have been proposed to improve the outcome of strabismus surgery for patients with TED including an intraoperative relaxed muscle positioning technique, the use of adjustable sutures, operating under monitored anesthetic care or local anesthesia, and simultatneous recession of tenon capsule.

To correct upper lid retraction, mullerotomy, Muller muscle extirpation, levator aponeurosis disinsertion/recession, and levator muscle myotomy with/without the use of adjustable or hangback sutures can be used. Full thickness blepharotomy has gained popularity because of its technical simplicity. Spacers may be required for advanced cases including hard palate/labial mucosal graft, dermis fat/strip graft, auricular/nasal septal cartilage, donor sclera and synthetic materials such as Medpor, Alloderm, aluminium foil, and polytetrafluoroethylene with or without intraoperative anti-metabolites such as mitomycin C and 5-fluorouracil. Transcutaneous/transconjunctival botulinum toxin A, steroid (triamcinolone acetonide) or filler (Restylane) injections have been used to alleviate lagophthalmos and exposure keratopathy before surgical intervention. In cases of severe corneal breakdown, tarsorrhaphy, gluing or corneal graft may be necessary.

Prognosis of thyroid eye disease

After achieving euthyroidism, up to 90% of lid retraction and 30% of restrictive myopathy improve, but proptosis rarely improves.[37] For patients with clinically evident TED (NOSPECS class 3 or above), the typical disease course continues for 18 to 36 months before it stabilizes.

Prevention of thyroid eye disease

Although the etiology/pathogenesis of Graves' disease/TED remains unknown, subjects at risk (family or personal history of autoimmune thyroid diseases, autoantibodies or

biochemical dysthyroidism) are advised to quit active and to avoid passive smoking (primary prevention to avoid occurrence).[37] Secondary prevention to avoid progression of subclinical TED involves early and tight control of dysthyroidism (in particular avoiding post-ablative hypothyroidism). Tertiary prevention to avoid development of vision-threatening complications requires early and judicious use of immunosuppressive therapies, orbital irradiation, and timely surgical rehabilitation.

The first thyroid eye clinic in Hong Kong

The first thyroid eye clinic in Hong Kong was established in fall 2010, and nearly 700 TED patients were managed in the past 6 years. Among them, 103 and 174 patients received oral and intravenous steroid, respectively. 77 required steroid-sparing agents (methotrexate or azathioprine) and 148 underwent orbital radiotherapy during systemic steroid treatment. 333 computed tomographies and 268 magnetic resonance imaging of the orbits were reviewed. 113 eyes were operated for orbital decompression in isolation or combination using transconjunctival fat removal (n=29), medial wall bone removal (n=63, 50 through the endoscopic transethmoidal approach), or lateral wall bone removal (n=79, 6 through the transforniceal conjunctival approach). We considered that the resource and research implication of TED in Hong Kong have been grossly underestimated.

Conclusion

TED is the most common cause of proptosis or lid retraction in adults and can present asymmetrically. At presentation, one in five patients with TED has normal thyroid function. Smoking cessation and early stabilisation of thyroid function are the most important primary and secondary TED prevention measure. Although most TED patients can be managed conservatively, patients with active, progressive or severe disease warrant specialist evaluation and consideration of treatment with intravenous steroid, orbital radiotherapy, and/or surgical decompression. More than one operation may be required to correct established or iatrogenic deformities.

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