Case 14

History of Present Illness

A 32-year-old white woman noted 2 months of periocular swelling, tearing, and redness of both eyes. She noted constant eye pressure behind both eyes worse with far eccentric upgaze. Closing the eyes did not improve the pain. Nonsteroidals did make the pain better but it did not resolve it. The pain had been the same without worsening or improvement over the past 2 months. She denied any visual loss or diplopia.

Past medical and ocular history None	*Past surgical history* None
Medications None	*Family history* Father—Hyperlipidemia, prostate cancer, skin cancer Mother—Hypothyroidism
Social history One glass of wine daily Never used tobacco Works as a cook at a military base	*Review of systems* Negative

Examination

Acuity with correction Right eye: 20/20-1 Left eye: 20/20
Pupils Equal, brisk, no APD
Intraocular pressure Right eye: 14 mmHg Left eye: 14 mmHg

M.S. Lee, K.B. Digre, *A Case-Based Guide to Eye Pain*,
https://doi.org/10.1007/978-3-319-65121-7_14

External exam Mild eyelid retraction both upper eye lids Margin reflex distance = 5.5 mm BE Hertel exophthalmometry 21 mm BE
Eye alignment and motility 25% symmetric elevator deficit BE Orthophoric in all gazes
Slit lamp examination 1+ chemosis and trace injection BE
Visual field Normal
Fundus examination Normal
Neurologic examination Normal

Discussion

Ophthalmic Perspective: Dr. Lee

Initially, one might assume that this is a dry eye case, which could be a contributing factor. However, close inspection of the figure shows mild eyelid edema LE greater than RE (Fig. 14.1) and some mild eyelid retraction BE. The combination of the eyelid edema and eyelid retraction really point toward thyroid eye disease (TED). The top limit of normal for Hertel exophthalmometry in a Caucasian woman is 20 mm, which would also make her suspicious for TED.

Now when I was in residency, I remember clearly being told that TED does not cause pain and if you see pain in a patient with orbital signs and symptoms, then you should think about something else. I held onto that mantra for a long time until I became a faculty member and started keeping track of the clinical activity score (CAS, Table 14.1), which is a standardized methodology for determining how active TED is. The first two points include spontaneous retrobulbar pain and pain on vertical gaze. Therefore, I have changed my tune that TED can definitely cause pain and is an indicator of activity.

I would have told this patient that the problem begins with an overactive immune system that attacks the thyroid gland as well as the orbital tissues including the eye muscles. Even if one removes the thyroid gland with surgery or radioactive iodine, the immune system is still overactive and can attack the eyes. In the majority of cases, the hyperthyroidism and orbital signs occur within 6 months of each other. There are definitely a significant number of Graves' patients who do not develop ophthalmopathy. In some cases, there may be isolated TED, and the patient is euthyroid. Normally, TED runs a course of getting worse, getting better, and then stabilizing but not returning back to normal baseline eye appearance, known as Rundle's curve. The time to reach stability is usually 1–3 years and can be several years in some cases. Sometimes it can be quite disfiguring and in others it may hardly be noticeable.

In mild cases, such as this, I would advise her to get thyroid function tests and a thyroid stimulating immunoglobulin (TSI). I would advise her to avoid smoke and secondhand smoke, which could worsen the course of the disease. I would ask her to

Fig. 14.1 External photographs show bilateral upper eyelid retraction. Normally, the upper eyelids cover the iris by about 1 mm. She also has very mild upper eyelid edema of the left upper eyelid

Table 14.1 Clinical activity score. One point for each and a score of 3+ = active TED

Spontaneous retrobulbar pain
Pain on attempted up- or downgaze
Redness of the eyelids
Swelling of the eyelids
Redness of the conjunctiva
Swelling of the conjunctiva
Inflammation of the caruncle or plica semilunaris

take selenium 100 micrograms twice daily and use artificial tears regularly. I would see her back at 4–6 month intervals sooner if she develops vision loss in either eye.

In moderate to severe cases, I might initiate IV steroids 500 mg weekly × 6 weeks followed by 250 mg weekly × 6 weeks. I might also give radiation therapy, 2000 cGy in 10 fractions. I am not a fan of giving oral steroids on a daily basis because I think that patients become very steroid-dependent. Recently, we have been trying pulsed oral prednisone 600 mg weekly by mouth for 6 weeks followed by 300 mg weekly for 6 weeks. For double vision, I either occlude one eye or blur one eye significantly. Patients that want to try a Fresnel prism can, but they understand that this may change with disease worsening. Hot off the presses in May 2017, a recent study in the New England Journal of Medicine showed that teprotumumab, a human monoclonal antibody inhibitor of IGF-IR, reduced proptosis and CAS in patients with active, moderate-to-severe ophthalmopathy compared to placebo. This could be a game changer and could conceivably reduce the time to stabilization of TED.

Once the patient stabilizes for at least 6 months and their CAS score is 2 or below, then I recommend surgical intervention, which can include orbital decompression, strabismus surgery, and eyelid repositioning (in this specific order). Some patients require all of these procedures and some only one or two.

Neurologic Perspective: Dr. Digre

TED is the most common cause of diplopia and I always look for evidence of thyroid eye disease if that is the chief complaint. Pain with thyroid eye disease is not rare and sometimes it can throw us off the track. For example, orbital myositis or orbital inflammatory disease can be in the differential diagnosis of thyroid eye disease. CT

and MR of the orbit are helpful if the typical tendon sparing is present. If the tendon is involved, it may be myositis. I also get orbital ultrasound when it is available, because the ultrasonographer can tell the difference between myositis and TED. Hashimoto's thyroiditis can also be associated with eye pain and TED. A thyroid receptor antibody can be helpful here. If patients have TED and migraine, migraines can be worsened by the thyroid disease and also the pain can be more pronounced.

TED patients do require a good eye examination. I get a baseline visual field as well as good measurements to follow the disease. Almost every thyroid patient gets dry eyes because of the proptosis and I frequently prescribe artificial tears. We order TSI and TRAB as well as thyroid tests.

Treatment of TED is so frustrating for patients because it is a waiting game for the thyroid eye disease to settle down before doing anything. In the meantime, follow the optic nerve function, and be sure the eyes stay lubricated. We try Fresnel prisms for diplopia or we fog a lens. Recently vitamin D has been reported to help.

For pain, we often use a non-steroidal anti-inflammatory since the pain is generally mild to moderate.

Non-ophthalmic/Non-neurologic Perspective

Graves' disease really requires a finding of either a high thyroid auto-antibody or an abnormal radioactive iodine uptake test. I usually start with thyroid function testing and a TSI along with the clinical exam to make the diagnosis. A CT or MRI of the orbit might reveal a large extraocular muscle but usually only if the patient has moderate disease and eye movement limitation. For whatever reason, there is a preferential involvement of the muscles in the following order: inferior, medial, superior, and lateral. So, if you see a scan that shows isolated lateral rectus enlargement, you would be suspicious that this may not be TED. Keep in mind that TED can cause vision loss and even blindness if the eye muscles compress the optic nerve, which requires urgent steroids and/or surgery. TED is best followed by either an orbital specialist or a neuro-ophthalmologist or anyone with strong familiarity and experience with the eye disease.

Follow Up

This patient had an elevated TSI and was diagnosed with Graves' disease. She is euthyroid on methimazole treatment. The literature supports that thyroidectomy causes less TED activity than radioactive iodine (RAI). She and her endocrinologist are debating the pros and cons of definitive treatment. If she opts for RAI, then I would recommend prednisone treatment before, during, and after to try to mitigate TED worsening. The patient is to follow up in 4–6 months sooner if she loses vision in either eye. *Final diagnosis: Thyroid eye disease*.

For Further Study

1. Mourits MP, Koornneef L, Wiersinga WM, et al. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy. Br J Ophthalmol. 1989;73:639–44.
2. Bothun ED, Scheurer RA, Harrison AR, Lee MS. Update on thyroid eye disease and management. Clin Ophthalmol. 2009;3:543–51.
3. Rao R, MacIntosh PW, Yoon MK, Lefebvre DR. Current trends in the management of thyroid eye disease. Curr Opin Ophthalmol. 2015;26(6):484–90.
4. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med. 2017;376:1748–61.