

# Review of thyroid eye disease in euthyroid state with periocular mucinosis



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## INTRODUCTION

Thyroid eye disease is a complex orbital inflammatory condition, which can be sight threatening, debilitating, and disfiguring. Among individuals with thyroid eye disease, 85% exhibit biochemical evidence of hyperthyroidism such as Graves disease, 10% have hypothyroidism such as Hashimoto thyroiditis, and 5% are euthyroid.<sup>1</sup> In individuals with thyroid eye disease with euthyroid state, there are no definitive diagnostic criteria and it is difficult to diagnose.<sup>2</sup> We evaluated the diagnostic value of skin biopsy in 5 patients with thyroid eye disease in the euthyroid state and biopsy-proven skin mucinosis.

## CASE PRESENTATIONS

### Case 1

A 55-year-old Korean man undergoing treatment for hypertension and diabetes mellitus visited the dermatology clinic, having a 3-month history of persistent left-eyelid febrile sensation and swelling. Physical examination revealed a localized, ill-demarcated, erythematous patch with swelling on the left upper eyelid. Skin biopsy of that eyelid was performed. Histopathologic analysis revealed amorphous material deposition between collagen bundles, with perivascular lymphocyte infiltration in the upper dermis. Alcian blue and thyroid-stimulating hormone staining was performed and revealed mucin deposition and a negative result for thyroid-stimulating hormone. Histopathologic findings were consistent with ocular mucinosis. Given the clinical and histologic findings, thyroid eye disease was

considered, and a thyroid function test and ocular magnetic resonance imaging were performed. Subclinical hyperthyroidism was revealed in the thyroid function test. Magnetic resonance imaging revealed thickening of extraocular muscle and tissue on the left side (Fig 1).

### Case 2

A 61-year-old Korean man visited the dermatology clinic, having a 3-month history of persistent left-eyelid swelling. An ill-demarcated erythematous patch with swelling was found on the left upper eyelid. Skin biopsy was performed and histopathologic analysis revealed amorphous material deposition between collagen bundles, with perivascular lymphocyte infiltration in the upper dermis. Alcian blue and thyroid-stimulating hormone staining results were positive. Given the clinical and histologic findings, thyroid eye disease was considered, and thyroid function and autoantibody tests were performed. Laboratory investigations did not reveal thyroid autoantibodies, and the thyroid function test result was normal. The patient received a diagnosis of euthyroid eye disease.

### Case 3

A 59-year-old Korean man visited the dermatology clinic, having a 3-month history of persistent swelling in both eyelids and the face, without overlying skin changes (Fig 2). Receiving a diagnosis of allergic contact dermatitis, he was treated with prednisolone and antihistamine for 1 month, without improvement. One month later, skin biopsy from the

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**Fig 1.** Left-sided extraocular muscle and soft tissue swelling on orbital magnetic resonance imaging (case 1).

left upper eyelid was performed. Histopathologic analysis revealed amorphous material deposition between collagen bundles, with perivascular lymphocyte infiltration in the upper dermis (Fig 3, A and B). Alcian blue (Fig 3, C) and thyroid-stimulating hormone staining results were positive. Given the clinical and histologic findings, thyroid eye disease was considered, and thyroid function and autoantibody tests were performed. Laboratory investigations did not reveal thyroid autoantibodies, and the thyroid function test result was normal. The patient received a diagnosis of euthyroid eye disease.

#### Case 4

A 63-year-old Korean man visited the dermatology clinic, having a 5-year history of persistent eyelid swelling with a mild itching sensation. Skin lesions were not found, except for swelling in both eyelids. Skin biopsy of the left upper eyelid was performed. Histopathologic analysis revealed amorphous material deposition between collagen bundles, with perivascular lymphocyte infiltration in the upper dermis. Alcian blue and thyroid-stimulating hormone staining results were positive. Thyroid-stimulating hormone staining in particular demonstrated a strong positive result (Fig 4, A and B). Given the clinical and histologic findings, thyroid eye disease was considered and a thyroid autoantibody test was performed. Laboratory investigations did not reveal thyroid autoantibodies, and the thyroid

function test result was normal. The patient received a diagnosis of euthyroid eye disease.

#### Case 5

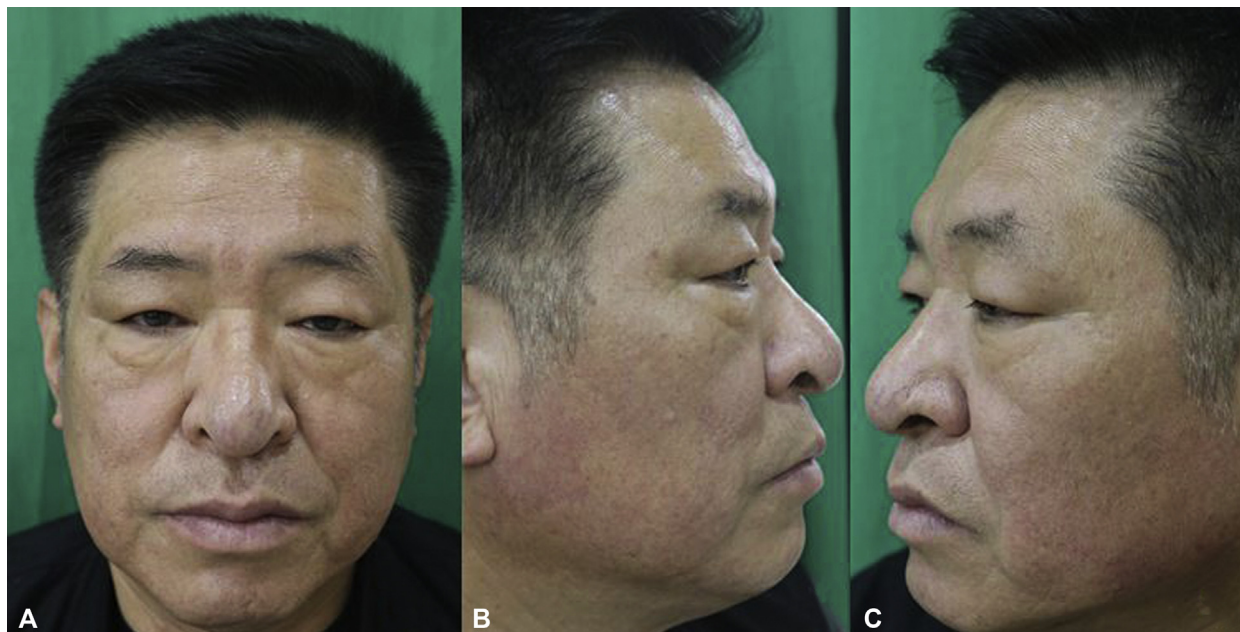
A 78-year-old Korean woman visited the dermatology clinic, having a 2-month history of persistent swelling in both eyelids, without skin lesions. She received a diagnosis of allergic contact dermatitis and was treated with prednisolone and antihistamines, without improvement for 6 months. Six months later, thyroid function and autoantibody tests were performed, which were positive for thyroid peroxidase antibody; the thyroid function test result was normal. The patient ultimately received a diagnosis of euthyroid eye disease.

#### SUMMARY OF REPORTED CASES

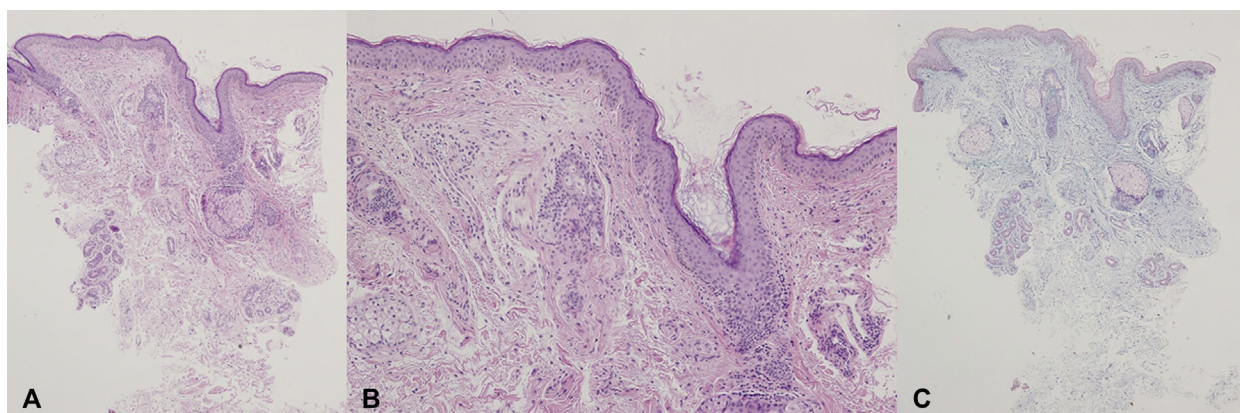
Clinical characteristics of these patients are summarized in Table 1. Four subjects underwent biopsy of the eyelid, with Alcian blue and thyroid-stimulating hormone staining. In addition, serum levels of triiodothyronine, thyroxine, and thyroid-stimulating hormone with thyroid autoantibody were measured in all patients. All patients exhibited eyelid swelling and an itching sensation. In particular, the patient described in case 1 had exophthalmos, periorbital swelling, and eye-movement restriction. He underwent ocular magnetic resonance imaging, which confirmed extraocular muscle and soft tissue swelling. Histopathologic assessment of the upper eyelid revealed deposition of mucin among the dermal collagen fibers in the dermis, along with lymphocytic infiltration in all cases, without affecting the epidermis. The patient described in case 4 demonstrated thyroid-stimulating hormone receptor overexpression on thyroid-stimulating hormone staining. Among the 5 patients, thyroid function test result was normal in 4, and the other individual (patient 1) exhibited subclinical hyperthyroidism. Additionally, 1 patient exhibited thyroid autoantibodies for thyroid peroxidase antibody, with normal thyroid function (patient 5). In cases 1 and 5, the patients received a diagnosis of thyroid eye disease according to current diagnostic criteria. However, considering clinical and histologic findings, with exclusion of other differential diagnoses, the other patients received a diagnosis of thyroid eye disease in the euthyroid state. All patients were treated with steroid pulse therapy and experienced partial improvement.

#### DISCUSSION

Thyroid eye disease is a complex orbital inflammatory condition that can exhibit variable symptoms,



**Fig 2.** Localized, ill-demarcated swelling on both upper eyelids (case 3). The left upper eyelid shows more prominent swelling (**A**, front; **B**, ventrolateral; and **C**, lateral).



**Fig 3.** Histopathologic finding of the patient described in case 3. **A**, The upper dermis had perivascular inflammation and spacing between the collagen bundles, as well as amorphous material deposition in the stroma. **B**, Perivascular lymphocytic infiltration was found in the upper dermis. **C**, Mucin deposition found on the whole layer of upper dermis. Overall upper dermis was more bluish than the deeper dermis. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**,  $\times 40$ ; **B**,  $\times 100$ . **C**, Alcian blue stain; original magnification:  $\times 40$ .)

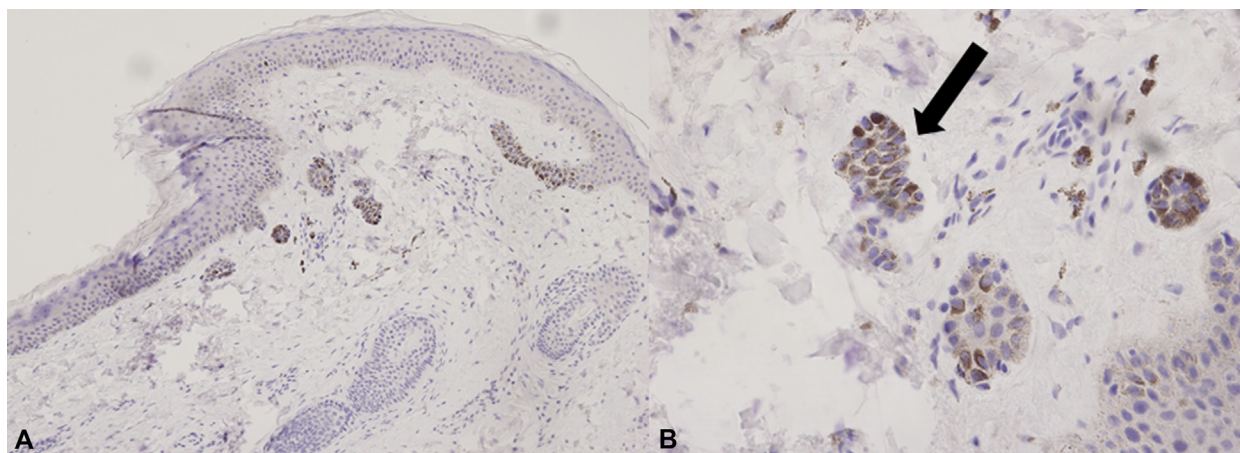
from eyelid swelling to some that are sight threatening.<sup>1</sup> It is caused by retro-orbital inflammation, in which thyroid-stimulating hormone receptor antibody and insulinlike growth factor-1 antibody are known to play important roles. Thyroid-stimulating hormone receptor antibody causes orbital fibroblast stimulation and stimulates adipogenesis, and insulinlike growth factor-1 antibody causes tissue swelling through T-cell activation.<sup>3</sup>

Diagnostic criteria for thyroid eye disease include 3 clinical requirements—positive result for a thyroid

function test, the presence of thyroid autoantibodies, and eye symptoms—of which at least 2 must be present to diagnose thyroid eye disease.<sup>1</sup> However, if thyroid function is normal and the thyroid function test result is without thyroid autoantibody, diagnosis becomes more challenging.

However, there have been an increasing number of reports describing thyroid eye disease in the euthyroid state, as well as absence of thyroid autoantibody, which is known as euthyroid eye disease. It is believed to be caused by autoimmunity





**Fig 4.** Histopathologic finding of the patient described in case 4. **A**, Thyroid stimulating hormone receptor, which was not found in normal skin; overexpression evident on the dermis. **B**, Brown-stained thyroid stimulating hormone receptor (arrow) was found in dermis. (**A** and **B**, Thyroid-stimulating hormone stain; original magnification:  $\times 400$ .)

**Table I.** Clinical characteristics of the enrolled patients

Case	Sex/age, years	Symptom	Onset	Thyroid state	Autoantibody	Mucin/TSH staining	Clinical features	
							Ocular symptoms	Radiologic findings
1	M/56	Swelling (L)	3 mo ago	Subclinical hyperthyroidism	—	+/-	Yes	Proved in ocular MRI
2	M/60	Swelling (L)	3 mo ago	Euthyroid	—	+/+	Yes	None
3	M/60	Swelling, itching (B)	1 y ago	Euthyroid	—	+/+	Yes	None
4	M/63	Swelling, itching (B)	5 y ago	Euthyroid	—	+/++	Yes	None
5	F/78	Swelling, itching (B)	8 mo ago	Euthyroid	TPO (+)	X/X	Yes	None

B, Both; F, woman; L, left; MRI, magnetic resonance imaging; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; X, biopsy not performed; —, negative; +, positive; ++, overexpression.

against the eye muscle antigen calsequestrin and orbital connective tissue antigen collagen XIII.<sup>4</sup> Because of the absence of diagnostic criteria for euthyroid eye disease, investigators have diagnosed the condition only according to ocular symptoms revealed in clinical ophthalmic examinations.<sup>2</sup> Ocular symptoms include eye movement difficulty, lid retraction, and radiographic abnormalities.

Not only are there no clear criteria for diagnosis but also the symptoms are vague and not severe. According to several studies investigating euthyroid eye disease, unilateral involvement (79.2%), low extraocular muscle involvement (25.0%), and lesser degrees of soft tissue inflammation are characteristic of euthyroid eye disease. In addition, swelling and eyelid retraction are the most common symptoms.<sup>2</sup>

We reported 5 patients with swelling and an itching sensation around the eyes who were treated for several months. We performed skin biopsy for 4 patients, all of whom had skin mucinosis, and in laboratory investigations the other patient's test

result was positive for thyroid peroxidase antibody autoantibody.

Histopathologically, thyroid dermatopathy, including thyroid eye disease, can exhibit skin mucinosis.<sup>5</sup> Therefore, biopsy-confirmed skin mucinosis can be helpful in diagnosing euthyroid eye disease. However, if the amount of mucin deposition is not prominent, careful histopathologic review is recommended. Also, other mucin deposition diseases, including cutaneous mucinosis, cutaneous lupus mucinosis, and granuloma annulare, should be excluded. In addition to skin mucinosis, a previous report described thyroid-stimulating hormone receptor, which was not shown in normal skin, and overexpression in thyroid dermatopathy.<sup>6</sup> Thyroid-stimulating hormone receptor overexpression in the patient described in case 4 increased the possibility of euthyroid eye disease.

The absence of proper diagnostic criteria with ambiguous symptoms makes diagnosis difficult, which in turn delays diagnosis and proper management. This delay can lead to severe eye symptoms,

such as exophthalmos, with structural changes in the eye muscle and soft tissues. After severe symptoms occur, treatment of thyroid eye disease is more difficult and can result in complications. Early detection of euthyroid eye disease facilitates treatment and improves prognosis. In addition to preexisting diagnostic criteria, additional biopsy-proven skin mucinosis and thyroid-stimulating hormone receptor overexpression can be valuable clues to diagnosis.

There have been several reported cases describing cutaneous manifestation of thyroid disease, including thyroid eye disease occurring before hyperthyroidism or Graves disease.<sup>5,7</sup> According to previous reports, cutaneous manifestations such as eyelid swelling can occur in the euthyroid state; therefore, skin biopsy can be considered a screening evaluation in cases of suspected euthyroid eye disease. In addition, periodic thyroid function tests in patients with suspected euthyroid eye disease who exhibit skin mucinosis in biopsy are necessary.

If there are prolonged symptoms, such as eyelid swelling and itching, the possibility of thyroid eye disease should be considered. To differentiate these symptoms, we recommend skin biopsy together with thyroid function and autoantibody tests. Without suspicion for other disease(s), normal laboratory findings with biopsy-proven skin mucinosis

increase the possibility of euthyroid eye disease. A periodic thyroid function test is recommended to predict the occurrence of hyperthyroidism in patients with euthyroid eye disease. Early detection using skin biopsy may improve the quality of life of patients with euthyroid eye disease by preventing progression of eye disease and reducing permanent complications.

#### REFERENCES

1. McAlinden C. An overview of thyroid eye disease. *Eye Vis (Lond)*. 2014;1:9.
2. Jang SY, Lee SY, Lee EJ, Yoon JS. Clinical features of thyroid-associated ophthalmopathy in clinically euthyroid Korean patients. *Eye (Lond)*. 2012;26(9):1263-1269.
3. Khoo TK, Bahn RS. Pathogenesis of Graves' ophthalmopathy: the role of autoantibodies. *Thyroid*. 2007;17(10):1013-1018.
4. McCorquodale T, Lahooti H, Gopinath B, Wall JR. Long-term follow-up of seven patients with ophthalmopathy not associated with thyroid autoimmunity: heterogeneity of autoimmune ophthalmopathy. *Clin Ophthalmol*. 2012;6:1063-1071.
5. Dhali TK, Chahar M. Thyroid dermopathy—a diagnostic clue of hidden hyperthyroidism. *Dermatoendocrinol*. 2015;6(1):e981078.
6. Rapoport B, Alsabeh R, Aftergood D, McLachlan SM. Elephantiasic pretibial myxedema: insight into and a hypothesis regarding the pathogenesis of the extrathyroidal manifestations of Graves' disease. *Thyroid*. 2000;10(8):685-692.
7. Tabasum A, Khan I, Taylor P, Das G, Okosieme OE. Thyroid antibody-negative euthyroid Graves' ophthalmopathy. *Endocrinol Diabetes Metab Case Rep*. 2016;2016:160008.