Thyroid-associated orbitopathy in patients with Hashimoto's thyroiditis: a case report

Wiesław Grzesiuk[1], Dorota Szydlarska[1], Aneta Pragacz[2], Ewa Bar-Andziak[1]

[1] Chair and Department of Internal Diseases and Endocrinology, Medical University, Warszawa, Poland

[2] Endocrinology Outpatient Clinic, Independent Public Healthcare Institution, Staszów, Poland

Abstract: Thyroid-associated orbitopathy is a set of ophthalmic symptoms resulting from an autoimmune process in which the swelling of extraocular tissues leads to exophthalmos either caused by hypersecretion and accumulation of glycosaminoglycans in the orbit fibroblasts or being the result of inflammatory processes in the oculomotor. These changes cause eyeball motility disturbances, keratopathy, and the pressure on the optical nerve. Thyroid-associated orbitopathy accompanies Graves' disease in most cases, whereas the Hashimoto's disease in only 5%. In the present case, other reasons for the exophthalmos such as tumors of the orbit and sinuses, intracranial tumors, aneurysms and vascular fistulas and orbit tissue inflammation of different etiology were excluded. Additional examinations showed that thyrotropin level was 26 μIU/ml (normal range 0.27–4.0), antithyroglobulin antibody level was 1763 IU/ml (normal range 0–115), antithyrotropin antibody level was 4.93 IU/l (normal range 0–1), and anti-thyroid peroxidase antibody level was 1609 IU/ml (normal range 0–35). An ultrasound examination showed a thyroid gland of 9.8 ml volume. A cytological presentation obtained by thin-needle aspiration biopsy demonstrated inflammatory infiltration of lymphocytes, indicating an autoimmune process. The iodine uptake after 24 hours was 9%. The active form of orbitopathy was diagnosed in the patient with hypothyreosis in the course of Hashimoto's disease. Moreover, the coexistence of another autoimmune disease, pernicious anemia was diagnosed. The administration of the methylprednisolone pulse therapy and levothyroxine caused remission of ophthalmic symptoms, and euthyreosis was obtained. Our report presents a rare coexistence of thyroid orbitopathy and Hashimoto's disease.

Key words: autoimmune disease, Hashimoto's disease, orbitopathy, thyroid antibodies

INTRODUCTION

Thyroid-associated orbitopathy (TAO) is a set of symptoms caused by an autoimmune process and related to orbit tissue. Ocular lesions in autoimmune thyroid diseases occur five times more often in women than in men (respectively, 16 and 2.9 cases per 100 000 annually). Their course and prognosis is so far worse in men [1]. Orbitopathy may occur simultaneously with the manifestation of hyperthyreosis or later (about 70%), before the manifestation of hypothyreosis (about 25%), in euthyreosis (<5%) and hypothyreosis (3–5%) [2]. In the pathogenesis of TAO, a significant role is assigned to the mutual antigen, which may be the thyroid stimulating hormone (TSH) receptor, located on thyroid cells, orbit muscles and fibroblasts. Antithyreotropin (anti-TSH) antibodies and autoreactive T-cell clones may trigger an inflammatory process in the orbit tissues. As a result, leukocytes secrete cytokines [3]. These substances stimulate fibroblasts to secrete and accumulate glycosaminoglycans, resulting in the swelling of extraocular tissues. The clinical manifestations of the described processes are exophthalmos, soft tissue swelling, eyeball motility disturbances, keratopathy and neuropathy of the optic nerve [4,5].

CASE REPORT

A patient, a 36-year-old, long-term smoker, was admitted to the hospital for a several-month history of eyeball pain, lacrimation, blurred and double vision. In the previous weeks, exophthalmos occurred. Symptoms of hyperthyreosis could not be traced back in the anamnesis, and on admittance, the patient did not show the symptoms typical for hypothyreosis. The patient's mother has been treated for a thyroid disorder. His physical examination showed flushing and swelling of the eyelids and lacrimal caruncle, conjunctival injection, and congestion of the palpebral conjunctiva. An ophthalmological examination showed a mild abduction deficiency. The degree of

Correspondence to:
Wiesław Grzesiuk, MD, PhD, Katedra i Klinika Chorób Wewnętrznych i Endokrynologii, Uniwersytet Medyczny, ul. Banacha 1a, 02-097 Warszawa, Poland, phone: +48-22-599-28-71, fax: +48-22-599-19-75, e-mail: grzesam@amwaw.edu.pl
Received: December 20, 2007. **Accepted in final form:** March 12, 2008.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2008; 118 (5): 318-321
Translated by Justyna Czekała, MA

exophthalmos in the Hertel exophtalmometer was 23 mm for the left eye and 20 mm for the right eye. Intraocular pressure was normal in both eyes. On a ten-point clinical activity score (CAS) of orbitopathy activity, changes were graded 8 points [5]. The patient reported that morbid obesity (body mass index 49 kg/m^2) had not importantly changed since adolescence. Six years earlier, he was diagnosed with pernicious anemia and he has been taking vitamin B_{12} since that time.

Laboratory examination results delivered by the patient showed TSH level 26 μIU/ml (normal range 0.27–4.2), antithyroglobulin (anti-Tg) antibody level was 1763 IU/ml (normal range 0–115), TSH receptor antibodies (TRAb) level measured in a manual luminescent TRAK human assay (Brahms) was defined as 4.93 IU/l (normal range 0–1), and antithyroid peroxidase antibodies (anti-TPO) level was 1609 IU/ml (normal range 0–35). Furthermore, a low level of high-density lipoprotein cholesterol fraction was reported – 30mg/dl (normal value in men >40), and C-reactive protein level increased to 24.95 mg/dl (normal range 0–10) and uric acid level increased to 8.0 mg/dl (normal range 2.8–7.0). An ultrasound examination showed a thyroid gland of 9.8 ml volume and of heterogeneous decreased echogenicity, without modular changes.

Magnetic resonance (MR) of the orbits showed bilateral exophthalmos caused mainly by the thickening of the medial rectus muscles (right 14 × 7 mm, left 13 × 7 mm) and the inferior rectus muscles (right 15 × 8 mm and left 14 × 7 mm). An ultrasound examination of the eyeballs and orbits demonstrated a significant widening of the oculomotor muscles and orbit tissue swelling. A cytological examination of both thyroid lobes, obtained by thin-needle aspiration biopsy performed under ultrasound control, demonstrated inflammatory infiltration composed of lymphocytes, indicating an autoimmune process. The iodine uptake after 24 hours was 9%. The active form of orbitopathy was diagnosed and the methylprednisolone pulse therapy was administered. Three doses of 1000 mg were given using drip infusion every third day and subsequently, oral prednisone 60 mg tapered by 10 mg per month was administered. The patient resolved to quit smoking.

Three-month therapy with glycocorticoids and levothyroxine 200 μg daily resulted in the remission of blurred and double vision. Only a minimal swelling of the conjuctiva occurred. The degree of exophthalmos was 23 mm in the left eye and remained unchanged in the right eye. Orbitopathy activity was graded 2 points on the CAS scale.

Thyreotropin and free hormone levels were within the reference values. The antibody levels decreased ie. anti-TPO to 330.8 IU/ml, anti-Tg to 396.6 IU/ml, and anti-TSH to 1.62 IU/l. The C-reactive protein level decreased to 6.2 mg/l.

A control MR examination of the orbits showed a decrease in the volume of the oculomotor muscles – the medial rectus muscles (right 4 × 11 mm, left 4.6 × 10 mm) and the inferior rectus muscles (right 9 × 6 mm, left 7 × 7.8 mm). A control ultrasonography of both orbits yielded normal results.

DISCUSSION

Thyroid-associated orbitopathy is a symptom typical for Graves' disease (GD) but it very rarely accompanies Hashimoto's disease (HD). In both of these diseases, anti-antithyroglobulin and anti-thyroid peroxidase antibodies are detected [6] and the long-acting thyroid stimulator protector (LATS-P). Therefore, these diseases have been qualified among autoimmune thyroid diseases (AITD). Identifying the LATS, immunoglobulin G, as an anti-TSH antibody stimulating or blocking the receptor explained the occurrence of hyperthyreosis or hypothyreosis in the course of AITD [6]. A frequent transformation of Graves' disease into Hashimoto's disease and the reverse is probably related to altered number of the respective blocking and stimulating antibodies. In the case of HD, one should not underestimate a role of cytotoxic T-lymphocytes which cause the destruction of thyroid cells [5]. In the year 2006, Eckstein and coworkers published a study in which they proved that higher TSH binding inhibitory immoglobulin levels indicate increased risk of the ophthalmopathy development [7]. A mutual factor causing hyperthyreosis and responsible for ocular abnormalities had been searched for a long time. Elucidation of the role of the TSH receptor, cytokines, adhesive molecules, the adipose tissue of the orbit, and the development of an animal model for ocular lesions contributed to the better understanding of the mechanisms of thyroid-associated orbitopathy development in the course of AITD [3,6,9].

Animal experiments proved that ophthalmic symptoms in the course of AITD may be evoked experimentally in the presence of antibodies blocking the TSH receptor. Some researchers claim that the occurrence of TAO depends on the sex and genetic predisposition and does not require the presence of antibodies stimulating the TSH receptor [10]. This discovery could explain the occurrence of ophthalmic symptoms in euthyreosis or hypothyreosis. On account of differences between the immune systems of people and animals (the experiments were performed on mice), we should be careful in the interpretion of the results of these studies [6]. The reports of the levels of antibodies stimulating and blocking the TSH receptor in patients with orbitopathy are ambiguous. The concept prevails that the blocking antibody levels are higher in subjects with a severe rather than only vaguely indicated form of TAO, whereas orbitopathy occurring in HD results from the inflammatory process in the orbit tissues triggered by the anti-TSH antibodies [2,6-8].

High levels of anti-TPO antibodies occur more often in Hashimoto's disease. However, they are detected also in different diseases and even in healthy people [11]. In the current case, as mentioned earlier, neither the anamnesis nor the physical examination indicated any thyroid disease. In regard to the anamnesis regarding the eye, the occurrence of exophthalmos, eyeball motility disturbances, and the increased TSH level, TAO was taken into consideration. On account of asymmetric exophthalmos, tumors of the orbit and sinuses, intracranial tumors, aneurisms and vascular fistulas and orbit tis-

sue inflammation of different etiology were also considered [12]. Typical MR abnormalities and the presence of antibodies against thyroid antigens settled the dilemma in favor of TAO diagnosis.

High anti-Tg and anti-TPO levels could indicate GD or HD. Increased TSH level, small thyroid volume of heterogeneous decreased echogenicity with low iodine uptake and the thin-needle biopsy result supported the diagnosis of HD.

Glucocorticoids and levothyroxine treatment resulted in a significant improvement of the clinical state. Smoking has been proven to worsen the course and prognosis of orbitopathy [5]. In this patient, smoking could have been one of the factors conducive to the manifestation of TAO. Hashimoto's disease may represent a component of the polyglandular autoimmune hypofunction syndrome. Therefore, in such patients, other autoimmune diseases should be expected such as pernicious anemia, adrenocortical insufficiency, hypoparathyroidism, type 1 diabetes, myasthenia gravis, hepatitis or albinism [13]. The patient has been diagnosed only with pernicious anemia. The presented case shows the rare coexistence of Hashimoto's disease and thyroid-associated orbitopathy in male patients.

REFERENCES

1. Krassas GE, Wiersinga WM. Thyroid eye disease: current concepts and the EUGOGO perspective. Thyroid International. 2005; 4: 3-4.
2. Shirakawa H, Amemiya T, Kasagi K, et al. Hashimoto disease with hyperthyroid ocular signs. Metab Pediat Ophthalmol. 1981; 5: 213-218.
3. Khoo TK, Bahn RS. Pathogenesis of Graves' ophthalmopathy: the role of autoantibodies. Thyroid. 2007; 17: 1013-1018.
4. Wiersinga WM, Perrot P, Kahaly GJ, et al. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. Eur J Endocrinol. 2006; 155: 387-389.
5. Jarząb B, Lewiński A, Płaczkiewicz-Jankowska E. Choroby tarczycy. In: Szczeklik A, ed. Choroby wewnętrzne. Kraków, Medycyna Praktyczna, 2005: 1033-1082.
6. Ludgate ME. Animal models of thyroid-associated ophthalmopathy. Thyroid. 2002; 12: 205-208.
7. Smith BR, Sanders J, Furmaniak J. The receptor antibodies. Thyroid. 2007; 17: 923-938.
8. Eckstein AK, Plicht M, Lax H, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab. 2006; 91: 3464-3470.
9. Nagayama Y. Animals models of Graves' hyperthyroidism. Thyroid. 2007; 17: 981-987.
10. Ludgate M. Animals models of Graves' disease. Eur J Endocrinol. 2000; 142: 1-8.
11. Niemczyk S, Panasiuk-Jarzyło E, Matuszkiewicz-Rowińska J, Niemczyk L. Ocena przydatności obecności przeciwciał przeciw tyreoperoksydazie (TPOAb) u chorych ze schyłkową niewydolnością nerek. Pol Arch Med Wewn. 2004; 111: 687-692.
12. Owecki M, Sowiński J. Oftalmopatia tarczycowa w przebiegu choroby Gravesa i Basedowa ze współistniejącym guzem prawego oczodołu i towarzyszącą hiperprolaktynemią – opis przypadku. Pol Arch Med Wewn. 2004; 112: 1335-1339.
13. Kozłowska J, Jabłońska J, Skórka B, et al. Współwystępowanie autoimmunologicznego zapalenia wątroby typu III i autoimmunologicznego zapalenia tarczycy typu III (choroba Gravesa i Basedowa). Pol Arch Med Wewn. 2004; 112: 1473-1478.